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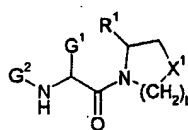
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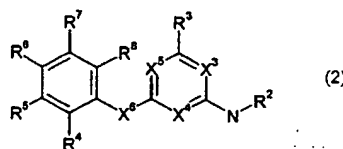
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(54) Title: INHIBITORS OF DIPEPTIDYL PEPTIDASE IV



(1)





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INHIBITORS OF DIPEPTIDYL PEPTIDASE IV

The present invention relates to novel compounds that are inhibitors of post-proline aminopeptidases. The compounds are useful as antiproliferative agents and in the treatment of, *inter alia*, type 2 diabetes and impaired glucose tolerance.

BACKGROUND

The enzyme dipeptidyl peptidase IV, herein abbreviated DP-IV (and elsewhere as DAP-IV or DPP-IV) and also known by the classification EC.3.4.14.5, is a serine protease that cleaves the N-terminal dipeptide from peptides that begin with the sequence H-Xaa-Pro (where Xaa is any amino acid, although preferably a lipophilic one, and Pro is proline). It will also accept as substrates peptides that begin with the sequence H-Xaa-Ala (where Ala is alanine). DP-IV was first identified as a membrane-bound protein. More recently a soluble form has been identified.

Initial interest in DP-IV focussed on its role in the activation of T lymphocytes. DP-IV is identical to the T cell protein CD26. It was proposed that inhibitors of DP-IV would be capable of modulating T cell responsiveness, and so could be developed as novel immunomodulators. It was further suggested that CD26 was a necessary co-receptor for HIV, and thus that DP-IV inhibitors could be useful in the treatment of AIDS.

Attention was given to the role of DP-IV outside the immune system. It was recognised that DP-IV has a key role in the degradation of several peptide hormones, including growth hormone releasing hormone (GHRH) and glucagon-like peptide-1 and -2 (GLP-1 and GLP-2). Since GLP-1 is known to have a potentiating effect on the action of insulin in the control of post-prandial blood glucose levels it is clear that DP-IV inhibitors might also be usefully employed in the treatment of type II diabetes and impaired glucose tolerance. At least two DP-IV inhibitors are currently undergoing clinical trials to explore this possibility.

Several groups have disclosed inhibitors of DP-IV. While some leads have been found from random screening programs, the majority of the work in this field has been directed towards the investigation of substrate analogues. Inhibitors of DP-IV that are substrate analogues are disclosed in, for example, US 5,462,928, US 5,543,396,

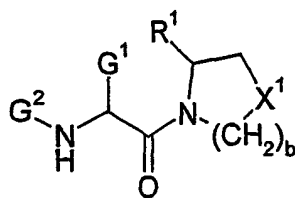
WO95/15309 (equivalent to US 5,939,560 and EP 0731789), WO98/19998 (equivalent to US 6,011,155), WO99/46272 and WO99/61431.

More recently a number of proteins have been found that share some of the enzymatic properties of DP-IV. Some, such as FAP and DPP-8, have sequence homology with DP-IV, while others, such as QPP, have no such homology but nevertheless mimic the aminodipeptidase activity of DP-IV. The physiological function of these newer proteases is still being investigated. FAP has been implicated in invasive processes such as cancer metastasis and endometriosis, and QPP appears to be involved in immune-cell apoptosis. It is also possible that some of these proteases share a common function. This redundancy would allow continuing normal physiological function in the event of a failure in the expression or function of one of the proteases.

In order to further define the roles of these newer proteases it is important to have the tools to manipulate selectively each one or the whole class. Therefore there exists a need for specific and potent inhibitors of each of these proteases, and also for potent non-specific inhibitors of the class of post-proline cleaving aminodipeptidases.

SUMMARY OF THE INVENTION

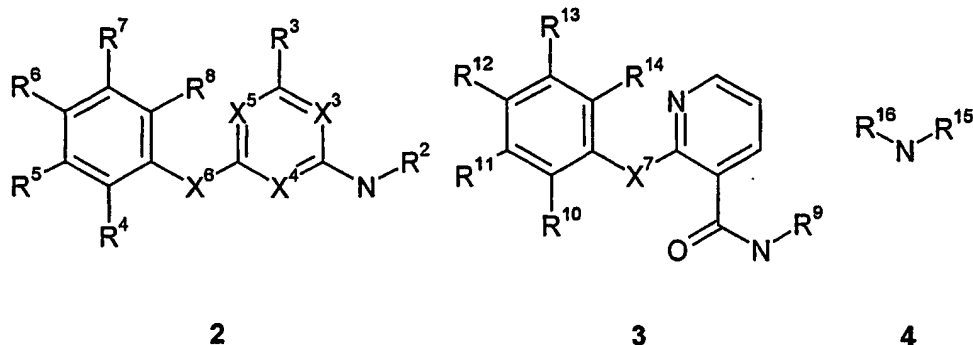
We disclose herein a series of novel compounds that are inhibitors of one or more post-proline cleaving proteases, and specifically compounds according to general formula 1.



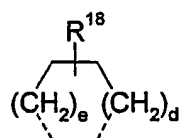
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In general formula 1, R^1 is H or CN, X^1 is O, S, CH_2 , CHF, CF_2 , $\text{CH}(\text{CH}_3)$, $\text{C}(\text{CH}_3)_2$ or $\text{CH}(\text{CN})$, and b is 1 or 2. G^1 is H or a group according to the formula $-\text{CH}_2-\text{X}^2-(\text{CH}_2)_a-$ G^3 and G^2 is H or a group according to the formula $-\text{CH}_2-(\text{CH}_2)_a-\text{G}^3$, provided that one of G^1 and G^2 is H and the other is not H. X^2 is O, S or CH_2 , and a is 0, 1 or 2, provided

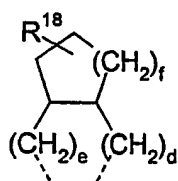
that when a is 1 then X^2 is CH_2 . G^3 is a group according to one of general formulae 2-4.



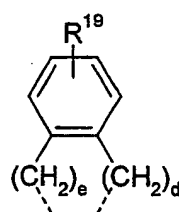
X^3 , X^4 and X^5 are either nitrogen N or CH, provided that at least two of X^3 , X^4 and X^5 are N. X^6 is either O or NH. R^2 is either H or alkyl. R^3 is selected from H, Cl, OH, O-alkyl, NH_2 , NH-alkyl and $N(alkyl)_2$. R^4 , R^5 , R^6 , R^7 and R^8 are selected from H, Br, Cl, F, CF_3 , alkyl, acyl, OH, O-alkyl, NH_2 , NH-alkyl, $N(alkyl)_2$, NO_2 , NH-acyl, CO_2H , CO_2 -alkyl, $CONH_2$, $CONH$ -alkyl, $CON(alkyl)_2$ and CN. X^7 is CH_2 , O, S or NH. R^9 is either H or alkyl. R^{10} , R^{11} , R^{12} , R^{13} and R^{14} are selected from H, Br, Cl, F, CF_3 , alkyl, acyl, OH, O-alkyl, NH_2 , NH-alkyl, $N(alkyl)_2$, NO_2 , NH-acyl, CO_2H , CO_2 -alkyl, $CONH_2$, $CONH$ -alkyl, $CON(alkyl)_2$ and CN. R^{15} and R^{16} are each independently H, alkyl, alkenyl, polyfluoroalkyl, aralkyl, aryl or CH_2-L-R^{17} , where L is a covalent bond, $CH=CH$, $C\equiv C$ or C_6H_4 , and R^{17} is H, alkyl or aryl, or R^{15} and R^{16} together are a group according to one of general formulae 5-7.



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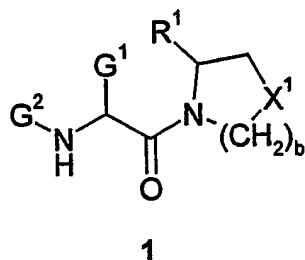
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R^{18} is H, alkyl, aryl, OH, O-alkyl, NH_2 , NH-alkyl or $N(alkyl)_2$, and R^{19} is H, alkyl, aryl, F, Cl, Br, CF_3 , OH, O-alkyl, NH_2 , NH-alkyl or $N(alkyl)_2$. The integers d and e are 0, 1, 2 or 3 such that $d+e$ is 3, 4 or 5, and f is 1, 2 or 3. When R^{15} and R^{16} are both H then X^1 may not be S or CH_2 if b is 1.

Preferred compositions are inhibitors of non-membrane associated post-proline cleaving proteases. The most preferred compositions are selective for non-membrane associated proteases (e.g. for example inhibitors of one or more of QPP, DPP-8 and/or DPP-9).

DETAILED DESCRIPTION OF THE INVENTION

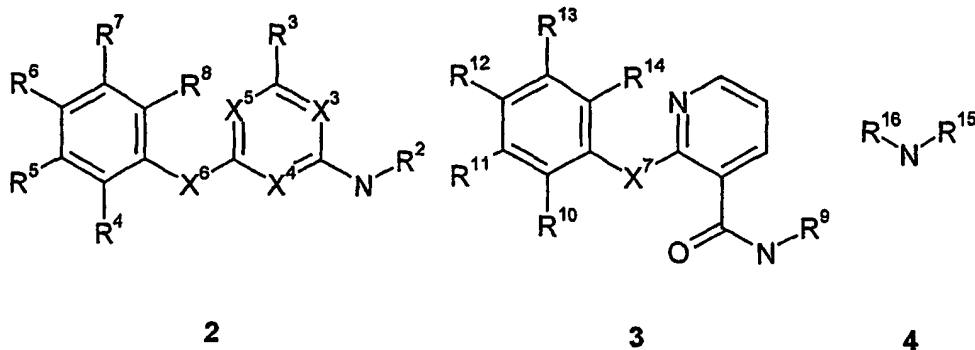
In a first aspect, the present invention relates to a series of novel α -amino acyl derivatives of saturated nitrogen-containing heterocycles according to general formula 1.



In general formula 1, the group R^1 is either a hydrogen atom H or a nitrile group CN. The group X^1 is selected from an oxygen atom O, a sulphur atom S, a methylene group CH_2 , a monofluoromethylene group CHF, a difluoromethylene group CF_2 , an ethylidene group $CH(CH_3)$, a 2-propylidene group $C(CH_3)_2$ and a cyanomethylene group $CH(CN)$. The integer b is either 1 or 2, such that the nitrogen-containing ring has 5 or 6 members.

The group G^1 is either H or a group according to the formula $-CH_2-X^2-(CH_2)_a-G^3$ and the group G^2 is either H or a group according to the formula $-CH_2-(CH_2)_a-G^3$, provided that one of G^1 and G^2 is H and the other is not H. The group X^2 is selected from O, S and CH_2 . The integer a is 0, 1 or 2, provided that when a is 1 then X^2 is CH_2 .

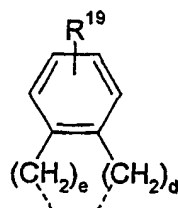
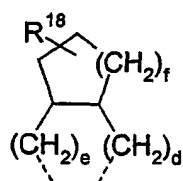
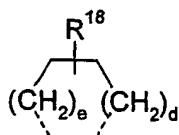
The group G^3 is selected from a group according to general formula 2, a group according to general formula 3 and a group according to general formula 4.



In general formula 2, the groups X^3 , X^4 and X^5 are selected from nitrogen N and methine CH, provided that at least two of X^3 , X^4 and X^5 are nitrogen. Preferably X^3 , X^4 and X^5 are all nitrogen. The group X^6 is selected from O and NH. R^2 is selected from H and alkyl. R^3 is selected from H, Cl, OH, O-alkyl, NH_2 , NH-alkyl and $N(alkyl)_2$. R^4 , R^5 , R^6 , R^7 and R^8 are independently selected from H, Br, Cl, F, CF_3 , alkyl, acyl, OH, O-alkyl, NH_2 , NH-alkyl, $N(alkyl)_2$, NO_2 , NH-acyl, CO_2H , CO_2 -alkyl, $CONH_2$, $CONH$ -alkyl, $CON(alkyl)_2$ and CN.

In general formula 3, the group X⁷ is selected from CH₂, O, S and NH. R⁹ is selected from H and alkyl. R¹⁰, R¹¹, R¹², R¹³ and R¹⁴ are independently selected from H, Br, Cl, F, CF₃, alkyl, acyl, OH, O-alkyl, NH₂, NH-alkyl, N(alkyl)₂, NO₂, NH-acyl, CO₂H, CO₂-alkyl, CONH₂, CONH-alkyl, CON(alkyl)₂ and CN.

In general formula 4, R¹⁵ and R¹⁶ are each independently selected from H, alkyl, alkenyl, polyfluoroalkyl, aralkyl, aryl and CH₂-L-R¹⁷, where L is selected from a covalent bond, CH=CH, C≡C and -C₆H₄- and R¹⁷ is selected from H, alkyl and aryl, or R¹⁵ and R¹⁶ together are a group selected from general formula 5, general formula 6 and general formula 7.



In these general formulae, the group R^{18} is selected from H, alkyl, aryl, OH, O-alkyl, NH_2 , NH-alkyl and $N(alkyl)_2$, and the group R^{19} is selected from H, alkyl, aryl, F, Cl, Br, CF_3 , OH, O-alkyl, NH_2 , NH-alkyl and $N(alkyl)_2$. The integers d and e are selected from 0, 1, 2 and 3 such that d+e is 3, 4 or 5, and the integer f is selected from 1, 2 and 3.

When R^{15} and R^{16} are both H then X^1 may not be S or CH_2 if b is 1.

The term alkyl, as used herein, denotes saturated hydrocarbon groups with between 1 and 10 carbon atoms, including straight-chain, branched and mono- and polycycloalkyl groups, such as methyl, ethyl, propyl, isopropyl, *n*-butyl, *tert*-butyl, cyclopentyl, cyclohexylmethyl, 2-cyclohexyl-2-propyl, bicyclo[2.2.2]octyl and the like.

The term alkenyl, as used herein, denotes monounsaturated hydrocarbon groups with between 2 and 10 carbon atoms, including straight-chain, branched and mono- and polycycloalkenyl groups, such as vinyl, allyl, methallyl, cyclohex-3-enyl and the like.

The term aryl, as used herein, denotes monocyclic and fused bicyclic aromatic groups, including carbocyclic groups, such as phenyl and naphthyl, and heteroaryl groups with up to three heteroatoms selected from nitrogen, oxygen and sulphur, such as pyrrolyl, furyl, thienyl, pyrazolyl, imidazolyl, oxazolyl, isothiazolyl, pyridyl, pyrimidinyl, indolyl, quinolinyl and the like. Unless otherwise specified, aryl groups may optionally be substituted with up to three groups independently selected from alkyl, OH, O-alkyl, Cl, F, Br, NH_2 , NH-alkyl, $N(alkyl)_2$, CO_2H , CO_2 -alkyl, $CONH_2$, CONH-alkyl, $CON(alkyl)_2$, NO_2 and CN.

The term aralkyl, as used herein, denotes alkyl groups that are substituted by, or fused to, one or more aryl groups, including benzyl, phenethyl, indanyl, fluorenyl and the like.

The term acyl, as used herein, denotes a group selected from H-CO, alkyl-CO, aryl-CO and aralkyl-CO, including formyl, acetyl, benzoyl, phenylacetyl and the like.

The term polyfluoroalkyl, as used herein, denotes an alkyl group wherein all the hydrogen atoms on one or more of the carbon atoms are replaced by fluorine atoms, including trifluoromethyl, 2,2,2-trifluoroethyl and the like.

In one preferred embodiment of the invention R^1 is H.

In another preferred embodiment of the invention R^1 is CN.

In another preferred embodiment of the invention X^1 is CH_2 .

In another preferred embodiment of the invention X^1 is S.

In another preferred embodiment of the invention b is 1.

In another preferred embodiment of the invention b is 2.

In another preferred embodiment of the invention a is 0.

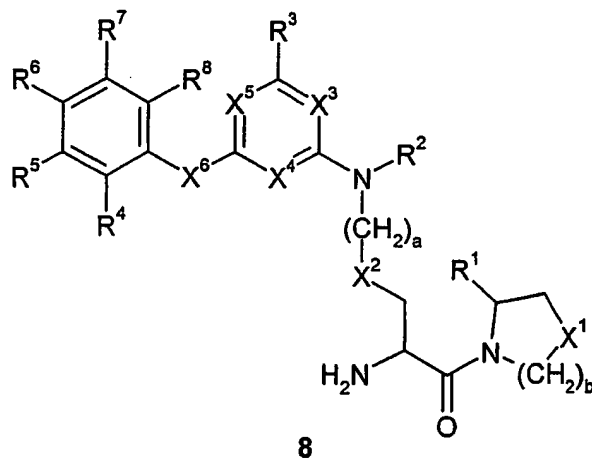
In another preferred embodiment of the invention a is 0 and X^2 is CH_2 .

In another preferred embodiment of the invention a is 1.

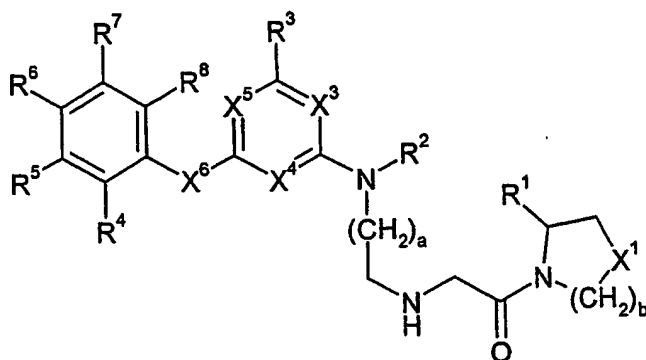
In another preferred embodiment of the invention a is 1 and X^2 is CH_2 .

In another preferred embodiment of the invention a is 2 and X^2 is CH_2 .

In another preferred embodiment of the invention the compound is a compound according to general formula 8.

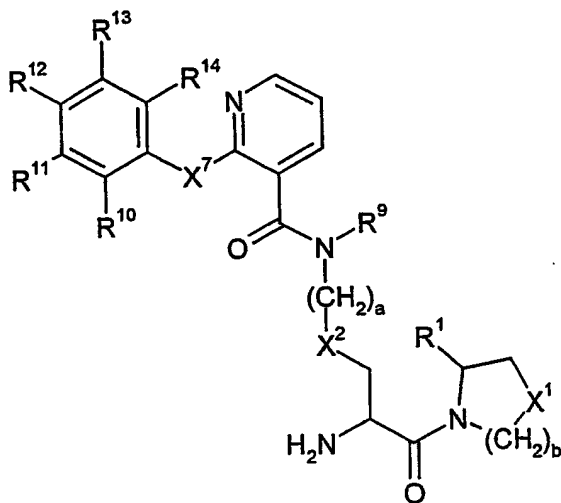


In another preferred embodiment of the invention the compound is a compound according to general formula 9.



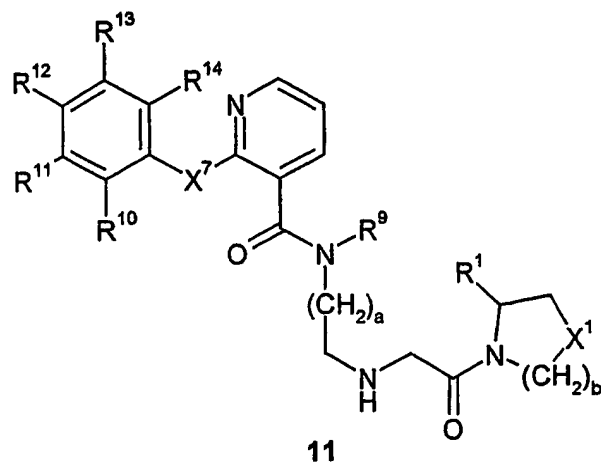
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In another preferred embodiment of the invention the compound is a compound according to general formula 10.

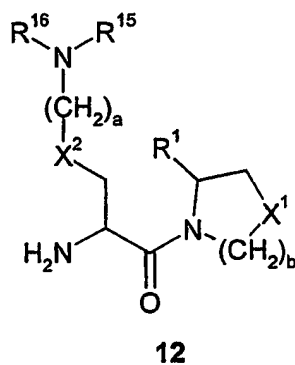


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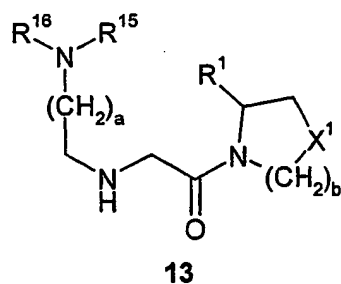
In another preferred embodiment of the invention the compound is a compound according to general formula 11.



In another preferred embodiment of the invention the compound is a compound according to general formula 12.



In another preferred embodiment of the invention the compound is a compound according to general formula 13.



It will be recognised that certain of the compounds within the scope of the present invention are capable of forming salts with suitable acids or bases. To the extent that such salts are pharmaceutically acceptable they are included within the scope of this invention

It will further be recognised that certain of the compounds within the scope of the present invention are capable of existing as optical isomers, such as enantiomers and diastereomers. All such optical isomers and mixtures thereof, including but not limited to racemates, are included within the scope of the invention.

The compounds of the present invention are inhibitors of post-proline cleaving proteases such as DPP-IV, QPP, FAP, DPP-8 (DPRP-1) and DPP-9 (DPRP-2). As such they may be useful in the treatment of diseases in which dysregulation of these enzymes or their endogenous substrates plays a role or the disease is ameliorated by inhibition of such enzymes. Accordingly, in further aspects, the present invention provides for the use of compounds according to the present invention in the preparation of pharmaceutical compositions, and for the use of such compositions as therapeutic agents.

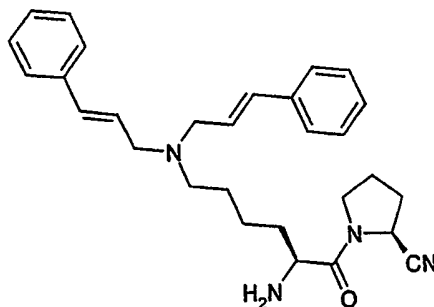
Preferred compositions which are inhibitors for QPP may have $G^2=H$, $b = 1$ or 2 and/or $a = 0$ or 1 . Further preferred compositions having $b=2$ include $G1$ groups having $a=0$ or 1 and X^2 is CH_2 . Further preferred compositions having $b=2$ have $X^1=CH_2$ or S , for example Example 38 of Table 2. Further preferred compositions having $b=1$ include $G1$ groups having $a=0$ or 1 and X^2 is CH_2 . Further preferred compositions having $b=1$ have $X^1= S$ or CH_2 or CF_2 , for example, Example 42 of Table 2.

The compounds of the present invention can be prepared by methods generally known in the art and illustrated in the following non-limiting examples.

EXAMPLES

EXAMPLE 1

(2S)-1-[N^{α},N^{α} -(Dicinnamyl)-L-lysiny]pyrrolidine-2-carbonitrile dihydrochloride



A. (*N*^ε-(*tert*-Butyloxycarbonyl)-*N*^α-(9-fluorenylmethyloxycarbonyl)-L-lysiny)-L-prolinamide

N^ε-(*tert*-Butyloxycarbonyl)-*N*^α-(9-fluorenylmethyloxycarbonyl)-L-lysine (5g, 10.7mmol) was dissolved in CH₂Cl₂ (100mL). The solution was cooled to 0°C, L-prolinamide (1.78g, 11.7mmol) and PyBOP® (6.7g, 12.8mmol) were added, and the pH adjusted to pH9 with triethylamine. After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (200mL). The solution was washed with 0.3M KHSO₄ (2 x 50mL), sat. NaHCO₃ (2 x 50mL), water (2 x 50mL) and brine (1 x 50mL), dried (Na₂SO₄) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 2% methanol, 98% chloroform) to give a colourless oil identified as (*N*^ε-(*tert*-butyloxycarbonyl)-*N*^α-(9-fluorenylmethyloxycarbonyl)-L-lysiny)-L-prolinamide (4.05g, 7.2mmol, 67%).

B. (2S)-1-(*N*^ε-(*tert*-Butyloxycarbonyl)-*N*^α-(9-fluorenylmethyloxycarbonyl)-L-lysiny)pyrrolidine-2-carbonitrile

(*N*^ε-(*tert*-Butyloxycarbonyl)-*N*^α-(9-fluorenylmethyloxycarbonyl)-L-lysiny)-L-prolinamide (3.95g, 7.02mmol) was dissolved in dry THF (100mL). The solution was cooled to 0°C, triethylamine (1.4g, 14mmol) was added followed by the slow addition of trifluoroacetic anhydride (2.97g, 14.1mmol). The pH was adjusted to pH9 with triethylamine. After 30min the reaction mixture was diluted with ethyl acetate (100mL), washed with water (1 x 50mL) and brine (1 x 50mL), dried (Na₂SO₄) and evaporated *in vacuo* to give an orange oil. The residue was purified by flash chromatography on silica gel (eluant: 60% pet ether, 40% ethyl acetate) to give a colourless oil identified as (2S)-1-(*N*^ε-(*tert*-butyloxycarbonyl)-*N*^α-(9-fluorenylmethyloxycarbonyl)-L-lysiny)pyrrolidine-2-carbonitrile (3.3g, 6.11mmol, 87%).

C. (2S)-1-(*N*^ε-(*tert*-Butyloxycarbonyl)-L-lysiny)pyrrolidine-2-carbonitrile

(2S)-1-(*N*^ε-(*tert*-Butyloxycarbonyl)-*N*^α-(9-fluorenylmethyloxycarbonyl)-L-lysiny)-pyrrolidine-2-carbonitrile (3.1g, 5.7mmol) was dissolved in THF (80mL). Diethylamine (20mL) was added. After 2h at room temperature the solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 90% chloroform, 7% methanol, 3% triethylamine) to give a colourless oil identified as (2S)-1-(*N*^ε-(*tert*-butyloxycarbonyl)-L-lysiny)pyrrolidine-2-carbonitrile (1.63g, 5.03mmol, 89%).

D. (2S)-1-(*N*^ε-(*tert*-Butyloxycarbonyl)-*N*^ω,*N*^ω-(dicinnamyl)-L-lysiny]pyrrolidine-2-carbonitrile

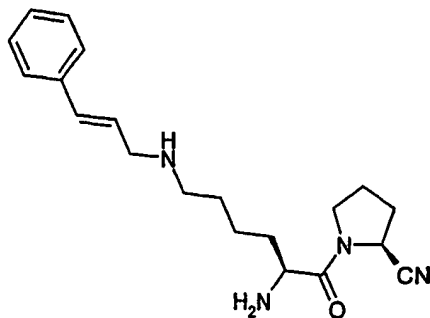
(2S)-1-(*N*^ε-(*tert*-Butyloxycarbonyl)-L-lysiny]pyrrolidine-2-carbonitrile (100mg, 0.31mmol) was dissolved in methanol (25mL). To this solution was added trans-cinnamaldehyde (170mg, 1.18mmol). After 30mins sodium triacetoxymethylborohydride (330mg, 1.56mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na₂SO₄) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 2% methanol, 98% chloroform) to give a colourless oil identified as (2S)-1-(*N*^ε-(*tert*-butyloxycarbonyl)-*N*^ω,*N*^ω-(dicinnamyl)-L-lysiny]pyrrolidine-2-carbonitrile (38mg, 0.068mmol, 11%). Further elution with 9% methanol, 90% chloroform and 1% acetic acid gave a colourless oil identified as (2S)-1-(*N*^ε-(*tert*-butyloxycarbonyl)-*N*^ω-(cinnamyl)-L-lysiny]pyrrolidine-2-carbonitrile (32mg, 0.073mmol, 12%)

E. (2S)-1-[*N*^ω,*N*^ω-(Dicinnamyl)-L-lysiny]pyrrolidine-2-carbonitrile dihydrochloride

(2S)-1-(*N*^ε-(*tert*-Butyloxycarbonyl)-*N*^ω,*N*^ω-(dicinnamyl)-L-lysiny]pyrrolidine-2-carbonitrile (32mg, 0.057mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as (2S)-1-[*N*^ω,*N*^ω-(dicinnamyl)-L-lysiny]pyrrolidine-2-carbonitrile dihydrochloride (37mg, 0.053mmol, 93%).

[M+H]⁺ = 457.3

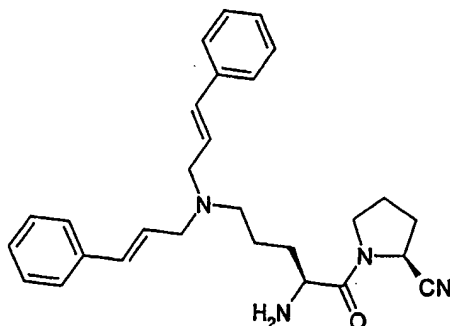
¹H NMR (CD₃OD): δ 1.35-1.55 (2H, m), 1.75-2.00 (2H, m), 2.05-2.23 (6H, m), 3.10-3.29 (4H, m), 3.61-3.68 (2H, m), 4.00-4.03 (4H, m), 4.20-4.30 (1H, m), 4.82-4.93 (1H, m), 6.34-6.39 (2H, m), 6.94 (2H, d, J = 5.8Hz), 7.31-7.37 (6H, m), 7.39-7.53 (4H, m) ppm.

EXAMPLE 2**(2S)-1-[N^o-(Cinnamyl)-L-lysiny]pyrrolidine-2-carbonitrile dihydrochloride****A. (2S)-1-[N^o-(Cinnamyl)-L-lysiny]pyrrolidine-2-carbonitrile dihydrochloride**

(2S)-1-(N^o-(*tert*-Butyloxycarbonyl)-N^o-(cinnamyl)-L-lysiny]pyrrolidine-2-carbonitrile (32mg, 0.057mmol). was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as (2S)-1-[N^o-(cinnamyl)-L-lysiny]pyrrolidine-2-carbonitrile dihydrochloride (37mg, 0.053mmol, 93%).

[M+H]⁺ = 341.5

¹H NMR (CD₃OD): δ 1.29-1.55 (2H, m), 1.72-1.80 (2H, m), 1.90-2.11 (2H, m), 2.16-2.29 (6H, m), 3.02-3.09 (2H, m), 3.65-3.69 (2H, m), 3.78-3.82 (2H, m), 4.23-4.27 (1H, m), 4.81-4.82 (1H, m), 4.91-4.99 (1H, m), 6.21-6.32 (1H, m), 6.86 (1H, d, J=6.1Hz), 7.26-7.35 (3H, m), 7.37-7.40 (2H, m) ppm.

EXAMPLE 3**(2S)-1-[N^o,N^o-(Dicinnamyl)-L-ornithiny]pyrrolidine-2-carbonitrile dihydrochloride**

A. (2S)-1-(*N*^ε-(*tert*-Butyloxycarbonyl)-L-ornithyl)pyrrolidine-2-carbonitrile

(2S)-1-(*N*^ε-(*tert*-Butyloxycarbonyl)-L-ornithyl)pyrrolidine-2-carbonitrile was prepared by the method described for the lysine derivative in Example 1.

B. (2S)-1-(*N*^ε-(*tert*-Butyloxycarbonyl)-*N*^ω,*N*^ω-(dicinnamyl)-L-ornithinyl)pyrrolidine-2-carbonitrile

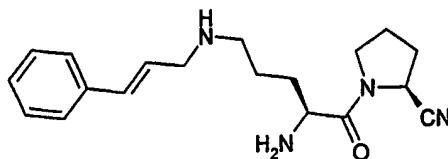
(2S)-1-(*N*^ε-(*tert*-Butyloxycarbonyl)-L-ornithinyl)pyrrolidine-2-carbonitrile (200mg, 0.65mmol) was dissolved in methanol (25mL). To this solution was added trans-cinnamaldehyde (180mg, 1.25mmol). After 30mins sodium triacetoxyborohydride (343mg, 1.63mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na₂SO₄) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography (eluant: 2% methanol, 98% chloroform) to give a colourless oil identified as (2S)-1-(*N*^ε-(*tert*-butyloxycarbonyl)-*N*^ω,*N*^ω-(dicinnamyl)-L-ornithinyl)-pyrrolidine-2-carbonitrile (77mg, 0.14mmol, 22%). Further elution with 9% methanol, 90% chloroform and 1% acetic acid gave a colourless oil identified as (2S)-1-(*N*^ε-(*tert*-butyloxycarbonyl)-*N*^ω-(cinnamyl)-L-ornithinyl)pyrrolidine-2-carbonitrile (78mg, 0.18mmol, 28%).

C. (2S)-1-[*N*^ω,*N*^ω-(Dicinnamyl)-L-ornithinyl]pyrrolidine-2-carbonitrile dihydrochloride

(2S)-1-(*N*^ε-(*tert*-Butyloxycarbonyl)-*N*^ω,*N*^ω-(dicinnamyl)-L-ornithinyl)pyrrolidine-2-carbonitrile (67mg, 0.12mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as (2S)-1-[*N*^ω,*N*^ω-(dicinnamyl)-L-ornithinyl]pyrrolidine-2-carbonitrile dihydrochloride (82mg, 0.12mmol, 100%).

$$[M+H]^+ = 443.3$$

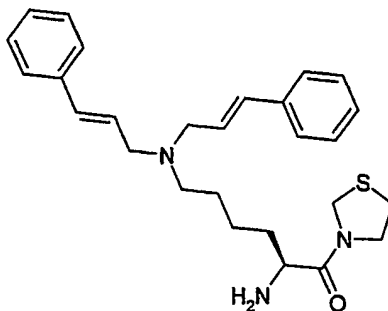
¹H NMR (CD₃OD): δ 1.98-2.12 (4H, m), 2.22-2.29 (4H, m), 3.27-3.31 (4H, m), 3.62-3.67 (2H, m), 3.96 (4H, d, J=7.5Hz), 4.30-4.40 (1H, m), 4.80-4.83 (1H, m), 6.34-6.41 (2H, m), 6.96 (2H, d, J=15.6Hz), 7.31-7.39 (6H, m), 7.49-7.53 (4H, m) ppm.

EXAMPLE 4**(2S)-1-[N^o-(Cinnamyl)-L-ornithinyl]pyrrolidine-2-carbonitrile dihydrochloride****A. (2S)-1-[N^o-(Cinnamyl)-L-ornithinyl]pyrrolidine-2-carbonitrile dihydrochloride**

(2S)-1-(N^o-(*tert*-Butyloxycarbonyl)-N^o-(cinnamyl)-L-ornithinyl)pyrrolidine-2-carbonitrile (71mg, 0.17mmol). was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as (2S)-1-[N^o-(cinnamyl)-L-ornithinyl]pyrrolidine-2-carbonitrile dihydrochloride (91mg, 0.16mmol, 100%).

$$[M+H]^+ = 327.5$$

¹H NMR (CD₃OD): δ 1.70-1.88 (2H, m), 1.97-2.01 (2H, m), 2.14-2.32 (4H, m), 3.08-3.13 (2H, m), 3.29-3.31 (3H, m), 3.68-3.71 (2H, m), 3.79-3.82 (2H, m), 4.29-4.31 (1H, m), 4.87-4.91 (1H, m), 6.29-6.31 (1H, m), 6.86 (1H, d, J=15.8Hz), 7.29-7.30 (3H, m), 7.44-7.48 (2H, m) ppm.

EXAMPLE 5**3-[N^o-N^o-(Dicinnamyl)-L-lysInyl]thiazolidine dihydrochloride**

A. 3-[*N*^α-(*tert*-Butyloxycarbonyl)-*N*^β-(9-fluorenylmethyloxycarbonyl)-L-lysiny]thiazolidine

N^α-(*tert*-Butyloxycarbonyl)-*N*^β-(9-fluorenylmethyloxycarbonyl)-L-lysine (2.73g, 6mmol) was dissolved in CH₂Cl₂ /DMF (9:1, 100mL). To this solution at 0°C were added 1-hydroxybenzotriazole hydrate (1.53g, 10mmol), water-soluble carbodiimide (1.34g, 7mmol), thiazolidine (1.28g, 18mmol) and N-methylmorpholine (1.0g, 10mmol). After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (100mL). The solution was washed with 0.3M KHSO₄ (2 x 25mL), sat. NaHCO₃ (2 x 25mL), water (2 x 25mL) and brine (1 x 25mL), dried (Na₂SO₄) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 75% ethyl acetate, 25% pet. ether) to give a white solid identified as 3-[*N*^α-(*tert*-butyloxycarbonyl)-*N*^β-(9-fluorenylmethyloxycarbonyl)-L-lysiny]thiazolidine (2.55g, 4.85mmol, 81%).

B. 3-[*N*^α-(*tert*-Butyloxycarbonyl)-L-lysiny]thiazolidine

3-[*N*^α-(*tert*-Butyloxycarbonyl)-*N*^β-(9-fluorenylmethyloxycarbonyl)-L-lysiny]thiazolidine (1.15g, 2.13mmol) was dissolved in acetonitrile (20mL). Diethylamine (5mL) was added. After 90min at room temperature the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (eluant: 90% chloroform, 7% methanol, 3% triethylamine) to give a pale yellow oil identified as 3-[*N*^α-(*tert*-butyloxycarbonyl)-L-lysiny]thiazolidine (530mg, 1.67mmol, 78%).

C. 3-(*N*^α-(*tert*-Butyloxycarbonyl)-*N*^β,*N*^β-(dicinnamyl)-L-lysiny)thiazolidine

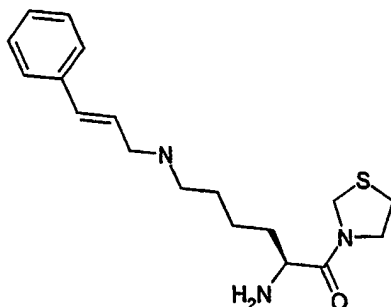
3-(*N*^α-(*tert*-Butyloxycarbonyl)-L-lysiny)thiazolidine (200mg, 0.6mmol) was dissolved in methanol (25mL). To this solution was added trans-cinnamaldehyde (400mg, 3.0mmol). After 30mins sodium triacetoxyborohydride (534mg, 2.54mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na₂SO₄) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 2% methanol, 98% chloroform) to give a colourless oil identified as 3-(*N*^α-(*tert*-butyloxycarbonyl)-*N*^β,*N*^β-(dicinnamyl)-L-lysiny)thiazolidine (139mg, 0.25mmol, 40%).

D. 3-[*N*^o,*N*^o-(Dicinnamyl)-L-lysiny]thiazolidine dihydrochloride

3-(*N*^o-(*tert*-Butyloxycarbonyl)-*N*^o,*N*^o-(di-cinnamyl)-L-lysiny]thiazolidine (139mg, 0.25mmol). was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a pale brown solid identified as 3-[*N*^o,*N*^o-(dicinnamyl)-L-lysiny]thiazolidine dihydrochloride (127mg, 0.24mmol, 96%).

[M+H]⁺ = 450.2

¹H NMR (CD₃OD): δ 1.49-1.55 (2H, m), 1.89-1.98 (4H, m), 3.01-3.30 (4H, m), 3.4-3.5 (4H, m), 3.7-3.9 (3H, m), 4.0-4.2 (3H, m), 4.2-4.8 (2H, br m), 6.38-6.44 (2H, m), 6.99-6.93 (2H, m), 7.34-7.37 (5H, m), 7.51-7.60 (4H, m) ppm.

EXAMPLE 6**3-[*N*^o,*N*^o-(Cinnamyl)-L-lysiny]thiazolidine dihydrochloride****A. 3-(*N*^o-(*tert*-Butyloxycarbonyl)-*N*^o,*N*^o-(cinnamyl)-L-lysiny]thiazolidine**

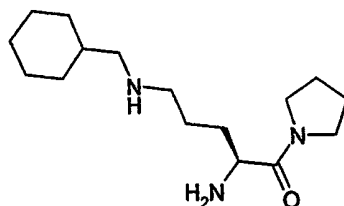
3-(*N*^o-(*tert*-Butyloxycarbonyl)-L-lysiny]thiazolidine (200mg, 0.6mmol) was dissolved in methanol (25mL). To this solution was added trans-cinnamaldehyde (400mg, 3.0mmol). After 30mins sodium triacetoxyborohydride (534mg, 2.54mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na₂SO₄) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 1% triethylamine, 5% methanol, 94% chloroform) to give a colourless oil identified as 3-(*N*^o-(*tert*-butyloxycarbonyl)-*N*^o,*N*^o-(cinnamyl)-L-lysiny]thiazolidine (215mg, 0.50mmol, 83%).

B. 3-[*N*^o,*N*^o-(Cinnamyl)-L-lysiny]thiazolidine dihydrochloride

3-(*N*^o-(*tert*-Butyloxycarbonyl)-*N*^o,*N*^o-(cinnamyl)-L-lysiny]thiazolidine (215mg, 0.5mmol). was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a pale brown solid identified as 3-[*N*^o,*N*^o-(cinnamyl)-L-lysiny]thiazolidine dihydrochloride (160mg, 0.40mmol, 79%).

$$[M+H]^+ = 334.4$$

¹H NMR (CD₃OD): δ 1.28-1.30 (1H, m), 1.51-1.53 (1H, m), 1.79-1.78 (1H, m), 1.93-1.98 (2H, m), 2.9-3.3 (5H, m), 3.6-3.8 (5H, m), 4.30-4.70 (5H, m), 6.2-6.3 (1H, m), 6.85-6.91 (1H, m), 7.1-7.7 (5H, m) ppm.

EXAMPLE 7**1-[*N*^o-(Cyclohexylmethyl)-L-ornithiny]pyrrolidine dihydrochloride****A. 1-[*N*^o-(Benzyloxycarbonyl)-*N*^o-(*tert*-butyloxycarbonyl)-L-ornithiny]pyrrolidine**

N^o-(Benzyloxycarbonyl)-*N*^o-(*tert*-butyloxycarbonyl)-L-ornithine (5.49g, 15mmol) was dissolved in CH₂Cl₂ /DMF (9:1, 100mL). To this solution at 0°C was added 1-hydroxybenzotriazole hydrate (3.37g, 22mmol), water-soluble carbodiimide (3.46g, 18mmol), pyrrolidine (1.28g, 18mmol) and N-methylmorpholine (2.0g, 20mmol). After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (200mL). The solution was washed with 0.3M KHSO₄ (2 x 50mL), sat. NaHCO₃ (2 x 50mL), water (2 x 50mL) and brine (1 x 50mL), dried (Na₂SO₄) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 90% ethyl acetate, 10% pet. ether) to give a colourless oil identified as 1-[*N*^o-(benzyloxycarbonyl)-*N*^o-(*tert*-butyloxycarbonyl)-L-ornithiny]pyrrolidine (5.15g, 12.3mmol, 82%).

B. 1-[N^ε-(*tert*-Butyloxycarbonyl)-L-ornithinyl]pyrrolidine

1-[N^ε-(Benzyloxycarbonyl)-N^ε-(*tert*-butyloxycarbonyl)-L-ornithinyl]pyrrolidine (2.15g, 5.13mmol) was dissolved in methanol (80mL). This solution was hydrogenated over 10% Pd/C (400mg). After 2h the catalyst was filtered off and washed with methanol (50mL). The combined filtrates were evaporated *in vacuo* to give an off white solid identified as 1-[N^ε-(*tert*-butyloxycarbonyl)-L-ornithinyl]pyrrolidine (1.35g, 4.74mmol, 94%).

C. 1-(N^ε-(*tert*-Butyloxycarbonyl)-N^δ-(cyclohexylmethyl)-L-ornithinyl)pyrrolidine

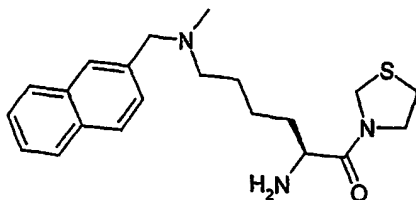
1-[N^ε-(*tert*-Butyloxycarbonyl)-L-ornithinyl]pyrrolidine (100mg, 0.35mmol) was dissolved in methanol (25mL). To this solution was added cyclohexanecarboxaldehyde (44mg, 0.39mmol). After 30mins sodium triacetoxyborohydride (148mg, 0.70mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na₂SO₄) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 1% triethylamine, 5% methanol, 94% chloroform) to give a colourless oil identified as 1-(N^ε-(*tert*-Butyloxycarbonyl)-N^δ-(cyclohexylmethyl)-L-ornithinyl)pyrrolidine (51mg, 0.18mmol, 52%).

D. 1-[N^δ-(Cyclohexylmethyl)-L-ornithinyl]pyrrolidine dihydrochloride

1-(N^ε-(*tert*-Butyloxycarbonyl)-N^δ-(cyclohexylmethyl)-L-ornithinyl)pyrrolidine (215mg, 0.5mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 1-[N^δ-(cyclohexylmethyl)-L-ornithinyl]pyrrolidine dihydrochloride (160mg, 0.40mmol, 79%).

[M+H]⁺ = 282.3

¹H NMR (CD₃OD): δ 0.93-1.24 (3H, m), 1.66-1.81 (15H, m), 2.50-2.70 (2H, m), 2.71-2.88 (2H, m), 3.2-3.48 (6H, m), 4.08 (1H, m), 8.35-8.38 (1H, m), 8.80-8.85 (1H, m) ppm.

EXAMPLE 8**3-[N^o-Me-N^o-(2-naphthylmethyl)-L-lysiny]thiazolidine dihydrochloride****A. N^α-(*tert*-Butyloxycarbonyl-N^o-benzyl-L-lysine methyl ester**

N^α-(*tert*-Butyloxycarbonyl-L-lysine methyl ester (6.1g, 22.2mmol) was dissolved in methanol (100mL). To this solution was added benzaldehyde (1.9g, 17.5mmol). After 2 hours sodium triacetoxyborohydride (5.8g, 27.3mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (200mL). This solution was washed with sat Na HCO₃ (1 x 50mL), water (12 x 50mL) and brine (1 x 50mL), dried (Na₂SO₄) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 1% acetic acid, 5% methanol, 94% chloroform) to give a colourless oil identified as N^α-(*tert*-butyloxycarbonyl-N^o- benzyl-L-lysine methyl ester (5.2g, 14.2mmol, 82%).

B. N^α-*tert*-Butyloxycarbonyl-N^o-benzyl-N^o-methyl-L-lysine methyl ester

N^α-*tert*-Butyloxycarbonyl-N^o-benzyl-L-lysine methyl ester (5.0g, 14.2mmol) was dissolved in methanol (100mL). To this solution was added formaldehyde (37% solution in water, 10mL). After 2 hours sodium triacetoxyborohydride (3.9g, 18.4mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (200mL). This solution was washed with sat. Na HCO₃ (1 x 50mL), water (12 x 50mL) and brine (1 x 50mL), dried (Na₂SO₄) and evaporated *in vacuo* to give a . colourless oil identified as N^α-*tert*-butyloxycarbonyl- N^o-benzyl-N^o-methyl-L-lysine methyl ester (5.2g, 14.2mmol, 100%).

C. N^α-*tert*-Butyloxycarbonyl-N^o-methyl-L-lysine methyl ester

N^α-*tert*-Butyloxycarbonyl-N^o-benzyl-N^o-methyl-L-lysine methyl ester (5.0g, 14.2mmol) was dissolved in methanol/water (9:1, 100mL). To this solution was added ammonium formate (1.6, 19.3mmol) and 10% palladium on charcoal (2g) . After 3 hours at 60 °C the catalyst was filtered off through celite and the residue washed with methanol (50mL). The combined filtrates were evaporated *in vacuo* and the residue was taken up in chloroform (200mL). This solution was washed with sat Na HCO₃ (1 x 50mL),

water (12 x 50mL) and brine (1 x 50mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a colourless oil identified as N^α -(*tert*-butyloxycarbonyl- N^ω -methyl-L-lysine methyl ester (3.48g, 12.5mmol, 93%).

D. N^α -*tert*-Butyloxycarbonyl- N^ω -(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)- N^ω -methyl-L-lysine methyl ester

N^α -*tert*-Butyloxycarbonyl- N^ω -methyl-L-lysine methyl ester (3.1g, 11.1mmol) was dissolved in dichloromethane (100mL). To this solution was added 1,1-dimethyl-2,2,2-trichloroethyl chloroformate (3.0g, 12.5mmol) and triethylamine (2.3g, 23mmol). After 18 hours at room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (200mL). This solution was washed with 0.3M KHSO_4 (1 x 50mL), sat NaHCO_3 (1 x 50mL), water (1 x 50mL) and brine (1 x 50mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil purified by flash chromatography on silica gel (eluant: 30% ethyl acetate, 70% pet. ether) to give colourless oil identified as N^α -(*tert*-butyloxycarbonyl- N^ω -(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)- N^ω -methyl-L-lysine methyl ester (3.28g, 6.98mmol, 63%).

E. N^α -*tert*-Butyloxycarbonyl- N^ω -(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)- N^ω -methyl-L-lysine

N^α -(*tert*-Butyloxycarbonyl- N^ω -(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)- N^ω -methyl-L-lysine methyl ester (3.1g, 6.6mmol) was dissolved in tetrahydrofuran (100mL). 1M Lithium hydroxide (7mL, 7.0mmol) was added. After 3 hours at room temperature the reaction mixture was diluted with ethyl acetate (150mL), washed with 1M HCl (1 x 50mL), water (1 x 50mL) and brine (1 x 50mL), dried (Na_2SO_4) and evaporated *in vacuo* to give colourless oil identified as N^α -(*tert*-butyloxycarbonyl- N^ω -(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)- N^ω -methyl-L-lysine (2.94g, 6.45mmol, 98%).

F. 3-(N^α -*tert*-Butyloxycarbonyl- N^ω -(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)- N^ω -methyl-L-lysinyI)thiazolidine

N^α -(*tert*-Butyloxycarbonyl- N^ω -(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)- N^ω -methyl-L-lysine (700mg, 1.51mmol) was dissolved in CH_2Cl_2 /DMF (9:1, 20mL). To this solution at 0°C were added 1-hydroxybenzotriazole hydrate (410mg, 3.0mmol), water-soluble carbodiimide (250mg, 1.3mmol), thiazolidine (170mg, 1.9mmol) and N-methylmorpholine (1.0g, 10mmol). After 18h at 0°C to room temperature the solvent

was removed *in vacuo* and the residue was taken up in ethyl acetate (70mL). The solution was washed with 0.3M KHSO₄ (1 x 25mL), sat. NaHCO₃ (1 x 25mL), water (1 x 25mL) and brine (1 x 25mL), dried (Na₂SO₄) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 50% ethyl acetate, 50% pet. ether) to give a white solid identified as 3-(N^α-*tert*-butyloxycarbonyl-N^ω-(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)-N^ω-methyl-L-lysiny])thiazolidine (758mg, 1.42mmol, 94%).

G. 3-(N^α-*tert*-Butyloxycarbonyl-N^ω-methyl-L-lysiny])thiazolidine

3-(N^α-*tert*-Butyloxycarbonyl-N^ω-(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)-N^ω-methyl-L-lysiny])thiazolidine (730mg, 1.36mmol) was dissolved in acetic acid (30mL). Zinc powder (200mg) was added. After stirring at room temperature for 18 hours the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). The solution was washed with sat. NaHCO₃ (1 x 25mL), water (1 x 25mL) and brine (1 x 25mL), dried (Na₂SO₄) and evaporated *in vacuo* to give a colourless oil identified as 3-(N^α-*tert*-butyloxycarbonyl-N^ω-methyl-L-lysiny])thiazolidine (438mg, 1.32mmol, 97%).

H. 3-[N^α-*tert*-Butyloxycarbonyl-N^ω-methyl-N^ω-(2-naphthylmethyl)-L-lysiny])thiazolidine

3-(N^α-*tert*-Butyloxycarbonyl-N^ω-methyl-L-lysiny])thiazolidine (50mg, 0.15mmol) was dissolved in 1,2-dichloroethane (20mL). To this solution was added 2-naphthaldehyde (26mg, 0.17mmol). After 2 hours sodium triacetoxyborohydride (36mg, 0.17mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na₂SO₄) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 4% methanol, 96% chloroform) to give a colourless oil identified as 3-[N^α-*tert*-butyloxycarbonyl-N^ω-methyl-N^ω-(2-naphthylmethyl)-L-lysiny])thiazolidine (51mg, 0.11mmol, 72%).

I. 3-[N^ω-Methyl-N^ω-(2-naphthylmethyl)-L-lysiny])thiazolidine dihydrochloride

3-[N^α-*tert*-Butyloxycarbonyl-N^ω-methyl-N^ω-(2-naphthylmethyl)-L-lysiny])thiazolidine (44mg, 0.093mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from

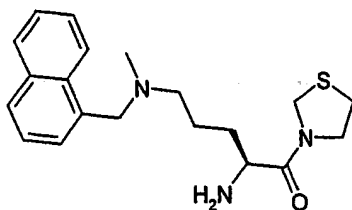
water to give a pale brown solid identified as 3-[*N*^o-methyl-*N*^o-(2-naphthylmethyl)-L-lysiny]thiazolidine dihydrochloride (37mg, 0.083mmol, 89%).

[M+H]⁺ = 372.2

¹H NMR (CD₃OD): δ 1.50-1.53 (2H,m), 1.91-1.98 (4H,m), 2.82 (3H,s), 3.08-3.19 (4H,m), 3.36-3.75 (5H,m), 4.32-4.47 (2H,m), 4.60-4.71 (2H,m), 7.55-7.59 (2H,m), 7.65-7.68 (1H,m), 7.90-8.00 (3H,m), 8.10-8.12 (1H,m) ppm.

EXAMPLE 9

3-[*N*^o-Methyl-*N*^o-(1-Napthylmethyl)-L-ornithyl]thiazolidine dihydrochloride



A. 3-[*N*-(*tert*-Butyloxycarbonyl)-*O*^o-methyl-L-glutamyl]thiazolidine

N-(*tert*-Butyloxycarbonyl)-*O*^o-methyl-L-glutamic acid (6.28g, 24mmol) was dissolved in CH₂Cl₂/DMF (9:1, 100ml). To this solution at 0°C were added 1-hydroxybenzotriazole hydrate (5.5g, 36mmol), water-soluble carbodiimide (5.38g, 28mmol), thiazolidine (2.48g, 28mmol) and *N*-methylmorpholine (3.0g, 30mmol). The mixture was stirred for 18h at 0°C to room temperature then the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (150ml). The solution was washed with 0.3M KHSO₄ (2 x 30ml), sat. NaHCO₃ (2 x 30ml), water (2 x 30ml) and brine (1 x 30ml), dried (Na₂SO₄) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 70% ethyl acetate, 30% pet. ether 60-80) to give a brown oil identified as 3-[*N*-(*tert*-butyloxycarbonyl)-*O*^o-methyl-L-glutamyl]thiazolidine (4.0g, 12mmol, 50%).

B. 3-[*N,N*-Di-(*tert*-butyloxycarbonyl)-*O*^o-methyl-L-glutamyl]thiazolidine

3-[*N*-(*tert*-Butyloxycarbonyl)-*O*^o-methyl-L-glutamyl]thiazolidine (3.2g, 9.6mmol) was dissolved in acetonitrile (20mL). Di-*tert*-butyl dicarbonate (3.14g, 14.4mmol) and 4-dimethylaminopyridine (235mg, 1.93mmol) were added. After 18 hours at room temperature further di-*tert*-butyl dicarbonate (3.14g, 14.4mmol) was added. After a further 3 days at room temperature the solvent was evaporated *in vacuo* the residue was purified by flash chromatography on silica gel (eluant: 70% ethyl acetate, 30% pet.

ether 60-80) to give a colourless oil identified as 3-[*N,N*-di-(*tert*-butoxycarbonyl)-*O*ⁿ-methyl-L-glutamyl]thiazolidine (2.0g, 4.63mmol, 48%).

C. 3-[*N,N*-Di-(*tert*-butoxycarbonyl)-L-glutamyl]thiazolidine

3-[*N,N*-di-(*tert*-butoxycarbonyl)-*O*ⁿ-methyl-L-glutamyl]thiazolidine (950mg, 2.22mmol) was dissolved in THF (50ml). 1M Lithium hydroxide (5.5ml, 5.5mmol) was added. The mixture was stirred for 1 hour at room temperature then the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (70ml). The solution was washed with 0.3M KHSO₄ (2 x 20ml), water (2 x 20ml) and brine (1 x 20ml), dried (Na₂SO₄) and evaporated *in vacuo* to give a colourless oil identified as 3-[*N,N*-di-(*tert*-butoxycarbonyl)-L-glutamyl]thiazolidine (912mg, 2.2mmol, 98%).

D. 3-[2-(*N,N*-Di-(*tert*-butoxycarbonyl)amino)-5-hydroxypentanoyl]thiazolidine

3-[*N,N*-Di-(*tert*-butoxycarbonyl)-L-glutamyl]thiazolidine (912mg, 2.2mmol) was dissolved in tetrahydrofuran (30 mL). This solution was cooled to -20 °C, *N*-methylmorpholine (300mg, 2.96mmol) and isobutyl chloroformate (387mg, 2.83mmol) were added. After 20 mins at -20 °C the reaction mixture was added to a solution of sodium borohydride (182mg, 4.8mmol) in water (5mL) at 0°C. After 1 hour the reaction mixture was diluted with ethyl acetate (150 mL). This solution was washed with water (1 x 20mL) and brine (1 x 20mL), dried (Na₂SO₄) and evaporated *in vacuo* to give a colourless oil identified as 3-[2-(*N,N*-di-(*tert*-butoxycarbonyl)amino)-5-hydroxypentanoyl]thiazolidine (800mg, 2.0mmol, 92%).

E. 3-[2-(*N,N*-Di-(*tert*-butoxycarbonyl)amino)-5-oxopentanoyl]thiazolidine

3-[2-*N,N*-(Di-*tert*-butoxycarbonyl)amino)-5-hydroxypentanoyl]thiazolidine (800mg, 2.0mmol) was dissolved in dichloromethane (50 mL). Dess-Martin periodinane (933mg, 2.2mmol) was added. After 1 hour at room temperature the reaction mixture was diluted with ethyl acetate (150 mL). This solution was washed with water (1 x 20ml) and brine (1 x 20ml), dried (Na₂SO₄) and evaporated *in vacuo* to give a colourless oil. Purified by flash chromatography on silica gel (eluant: 50% ethyl acetate, 50% pet. ether 60-80) to give a colourless oil identified as 3-[2-(*N,N*-di-(*tert*-butoxycarbonyl)amino)-5-oxopentanoyl]thiazolidine (210mg, 0.52mmol, 26%).

F. 3-[N,N-Di-(*tert*-butyloxycarbonyl-*N*^o-methyl-*N*^o-(1-naphthylmethyl)-L-ornithyl)]thiazolidine

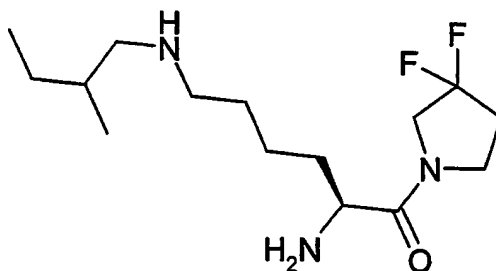
3-[N,N-Di-(*tert*-butyloxycarbonyl)amino-5-oxopentanoyl]thiazolidine was dissolved in 1,2-dichloroethane (20mL). To this solution was added N-methyl-1-naphthylmethylamine. After 2 hours sodium triacetoxyborohydride was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na₂SO₄) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel to give a colourless oil identified as 3-[N,N-di-(*tert*-butyloxycarbonyl-*N*^o-methyl-*N*^o-(1-naphthylmethyl)-L-ornithyl]thiazolidine.

G. 3-[*N*^o-Methyl-*N*^o-(1-Naphthylmethyl)-L-ornithyl]thiazolidine dihydrochloride

3-[N,N-Di-(*tert*-butyloxycarbonyl-*N*^o-methyl-*N*^o-(1-naphthylmethyl)-L-ornithyl]thiazolidine was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a pale brown solid identified as 3-[*N*^o-Me,*N*^o-(1-naphthylmethyl)-L-ornithyl]thiazolidine dihydrochloride.

EXAMPLE 10

3,3-Difluoro-1-[*N*^o-(2-methylbutyl)-L-lysiny]pyrrolidine dihydrochloride



A. 1-(*tert*-Butyloxycarbonyl)-3-pyrrolidone

(3*R*)-1-(*tert*-Butyloxycarbonyl)-3-hydroxypyrrolidine (980mg, 5.3mmol) was dissolved in CH₂Cl₂ (40ml). Dess-Martin periodinane (2.5g, 5.8mmol) was added. The mixture was stirred for 3 hours at room temperature then the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (300ml). The solution was washed with sat. NaHCO₃, water and brine, dried (Na₂SO₄) and evaporated *in vacuo* to give a

colourless oil. The residue was purified by flash chromatography on silica gel (eluant: 20% ethyl acetate, 80% pet. ether 60-80) to give a colourless oil identified as 1-(*tert*-butyloxycarbonyl)-3-pyrrolidone (842mg, 4.6mmol, 87%).

B. 1-(*tert*-Butyloxycarbonyl)-3,3-difluoropyrrolidine

1-(*tert*-Butyloxycarbonyl)-3-pyrrolidone (810mg, 4.4mmol) was dissolved in CH₂Cl₂ (30ml). (Diethylamino)sulphur trifluoride (2.2g, 13.7mmol) was added to this solution at 0°C. The mixture was stirred for 18 hours at 0°C to room temperature then carefully poured into sat. NaHCO₃ (100ml). The mixture was stirred for 15min then extracted with CH₂Cl₂. The organic extract was washed with water and brine, dried (Na₂SO₄) and evaporated *in vacuo* to give an orange oil. The residue was purified by flash chromatography (eluant: 10% ethyl acetate, 90% pet. ether 60-80) to give a colourless oil identified as 1-(*tert*-butyloxycarbonyl)-3,3-difluoropyrrolidine (580mg, 2.8mmol, 64%).

C. 3,3-Difluoropyrrolidine hydrochloride

1-(*tert*-Butyloxycarbonyl)-3,3-difluoropyrrolidine (540mg, 2.6mmol) was dissolved in 4M HCl/dioxan (30ml). The solution was stirred for 1 hour at room temperature then the solvent was removed *in vacuo* to give an off white solid identified as 3,3-difluoropyrrolidine hydrochloride (370mg, 2.6mmol, 100%).

D. 1-[N^t-(*tert*-Butyloxycarbonyl)-N^p-(9-fluorenylmethyloxycarbonyl)-L-lysiny]-3,3-difluoropyrrolidine

N^t-(*tert*-Butyloxycarbonyl)-N^p-(9-fluorenylmethyloxycarbonyl)-L-lysine (1.14g, 2.4mmol) was dissolved in CH₂Cl₂ /DMF (9:1, 100ml). To this solution at 0°C were added 1-hydroxybenzotriazole hydrate (394mg, 2.9mmol), water-soluble carbodiimide (680mg, 3.4mmol), 3,3-difluoropyrrolidine hydrochloride (380mg, 2.43mmol) and N-methylmorpholine (400mg, 4mmol). The mixture was stirred for 18h at 0°C to room temperature then the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (200ml). The solution was washed with 0.3M KHSO₄, sat. NaHCO₃, water and brine, dried (Na₂SO₄) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 65% ethyl acetate, 35% pet. ether 60-80) to give a white solid identified as 1-[N^t-(*tert*-butyloxycarbonyl)-N^p-(9-fluorenylmethyloxycarbonyl)-L-lysiny]-3,3-difluoropyrrolidine (1.0g, 1.8mmol, 75%).

E. 1-[N^ε-(*tert*-Butyloxycarbonyl)-L-lysiny]-3,3-difluoropyrrolidine

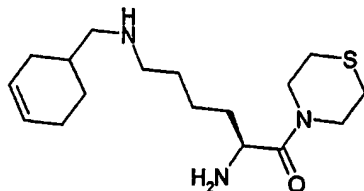
1-[N^ε-(*tert*-Butyloxycarbonyl)-N^ω-(9-fluorenylmethyloxycarbonyl)-L-lysiny]-3,3-difluoropyrrolidine (1.01g, 1.8mmol) was dissolved in THF (20ml). Diethylamine (5ml) was added. The mixture was stirred for 3 hours at room temperature then the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (eluant: 90% chloroform, 7% methanol, 3% triethylamine) to give a pale yellow oil identified as 1-[N^ε-(*tert*-butyloxycarbonyl)-L-lysiny]-3,3-difluoropyrrolidine (598mg, 1.78mmol, 99%).

F. 1-[N^ε-(*tert*-Butyloxycarbonyl)-N^ω-(2-methylbutyl)-L-lysiny]-3,3-difluoropyrrolidine

1-[N^ε-(*tert*-Butyloxycarbonyl)-L-lysiny]-3,3-difluoropyrrolidine was dissolved in 1,2-dichloroethane (20mL). To this solution was added 2-methylbutanal. After 2 hours sodium triacetoxyborohydride was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na₂SO₄) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel to give a colourless oil identified as 1-[N^ε-(*tert*-butyloxycarbonyl)-N^ω-(2-methylbutyl)-L-lysiny]-3,3-difluoropyrrolidine.

G. 3,3-Difluoro -1-[N^ω-(2-methylbutyl)-L-lysiny] pyrrolidine dihydrochloride

1-[N^ε-(*tert*-Butyloxycarbonyl)-N^ω-(2-methylbutyl)-L-lysiny]-3,3-difluoropyrrolidine was dissolved in 4M HCl/dioxan (20ml). The mixture was stirred for 1 hour at room temperature then the solvent was removed *in vacuo* to give a colourless oil identified as 3,3-difluoro-1-[N^ω-(2-methylbutyl)-L-lysiny]pyrrolidine dihydrochloride.

EXAMPLE 11**1-[N^ω-(3-Cyclohexenylmethyl)-L-lysiny]thiomorpholine dihydrochloride**

A. 3-[*N*^ε-(*tert*-Butyloxycarbonyl)-*N*^ω-(9-fluorenylmethyloxycarbonyl)-L-lysiny]thiomorpholine

N^ε-(*tert*-Butyloxycarbonyl)-*N*^ω-(9-fluorenylmethyloxycarbonyl)-L-lysine (2.5g, 5.34mmol) was dissolved in CH₂Cl₂ /DMF (9:1, 100mL). To this solution at 0°C were added 1-hydroxybenzotriazole hydrate (1.44g, 10.6mmol), water-soluble carbodiimide (1.35g, 6.5mmol), thiomorpholine (710mg, 6.9mmol) and N-methylmorpholine (800mg, 8mmol). After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (100mL). The solution was washed with 0.3M KHSO₄ (2 x 25mL), sat. NaHCO₃ (2 x 25mL), water (2 x 25mL) and brine (1 x 25mL), dried (Na₂SO₄) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 75% ethyl acetate, 25% pet. ether) to give a white solid identified as 3-[*N*^ε-(*tert*-butyloxycarbonyl)-*N*^ω-(9-fluorenylmethyloxycarbonyl)-L-lysiny]thiomorpholine (2.70g, 4.88mmol, 91%).

B. 3-[*N*^ε-(*tert*-Butyloxycarbonyl)-L-lysiny]thiomorpholine

3-[*N*^ε-(*tert*-Butyloxycarbonyl)-*N*^ω-(9-fluorenylmethyloxycarbonyl)-L-lysiny]thiomorpholine (2.6g, 4.7mmol) was dissolved in tetrahydrofuran (20mL). Diethylamine (5mL) was added. After 90min at room temperature the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (eluant: 90% chloroform, 7% methanol, 3% triethylamine) to give a pale yellow oil identified as 3-[*N*^ε-(*tert*-butyloxycarbonyl)-L-lysiny]thiomorpholine (1.2g, 3.637mmol, 77%).

C. 3-[*N*^ε-(*tert*-Butyloxycarbonyl)-*N*^ω-(3-cyclohexenylmethyl)-L-lysiny]thiomorpholine

3-(*N*^ε-(*tert*-Butyloxycarbonyl)-L-lysiny)thiomorpholine (150mg, 0.45mmol) was dissolved in methanol (25mL). To this solution was added 3-cyclohexenecarboxaldehyde (400mg, 0.45mmol). After 30mins sodium triacetoxymethylborohydride (150mg, 0.71mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na₂SO₄) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 1% acetic acid, 9% methanol, 90% chloroform) to give a colourless oil identified as 3-(*N*^ε-(*tert*-butyloxycarbonyl)-*N*^ω-(3-cyclohexenylmethyl)-L-lysiny)thiomorpholine (66mg, 0.12mmol, 26%).

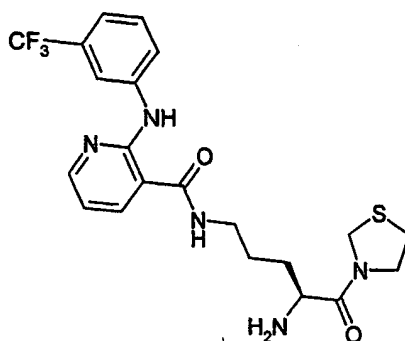
D. 1-[N^o-(3-Cyclohexenylmethyl)-L-lysiny]thiomorpholine dihydrochloride

3-(N^o-(*tert*-Butyloxycarbonyl)-N^o-(3-cyclohexenylmethyl)-L-lysiny]thiomorpholine (66mg, 0.12mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 1-[N^o-(3-cyclohexenylmethyl)-L-lysiny]thiomorpholine dihydrochloride (62mg, 0.12mmol, 100%).

$$[M+H]^+ = 326.2$$

EXAMPLE 12

(2S)-1-[N^o-(2-(3'-trifluoromethylanilino)pyridyl-3-carbonyl)-L-ornithyl]thiazolidine dihydrochloride

**A. 3-[N^o-*tert*-Butyloxycarbonyl-N^o-(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)-L-ornithyl]thiazolidine**

N^o-(*tert*-Butyloxycarbonyl)-N^o-(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)-L-ornithine (2.5g, 5.9mmol) was dissolved in CH₂Cl₂ /DMF (9:1, 30mL). To this solution at 0°C were added 1-hydroxybenzotriazole hydrate (1.6g, 11.9mmol), water-soluble carbodiimide (1.4g, 7.6mmol), thiazolidine (650mg, 7.3mmol) and N-methylmorpholine (2.0g, 20mmol). After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (70mL). The solution was washed with 0.3M KHSO₄ (1 x 25mL), sat. NaHCO₃ (1 x 25mL), water (1 x 25mL) and brine (1 x 25mL), dried (Na₂SO₄) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 70% ethyl acetate, 30% pet. ether) to

give a colourless oil identified as 3-[N^α-*tert*-butyloxycarbonyl-N^ω-(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)-L-ornithyl]thiazolidine (758mg, 1.42mmol, 94%).

B. 3-(N^α-*tert*-Butyloxycarbonyl- L-ornithinyl)thiazolidine

3-[N^α-*tert*-Butyloxycarbonyl-N^ω-(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)-L-ornithyl]thiazolidine (130mg, 0.26mmol) was dissolved in acetic acid (30mL). Zinc powder (100mg) was added. After stirring at room temperature for 18 hours the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). The solution was washed with sat. NaHCO₃ (1 x 25mL), water (1 x 25mL) and brine (1 x 25mL), dried (Na₂SO₄) and evaporated *in vacuo* to give a colourless oil identified as 3-(N^α-*tert*-butyloxycarbonyl-L-ornithinyl)thiazolidine (80mg, 0.26mmol, 100%).

C. 3-[N^α-*tert*-Butyloxycarbonyl-N^ω-(2-(3'-trifluoromethylanilino)pyridyl-3-carbonyl)-L-ornithinyl]thiazolidine

3-(N^α-*tert*-Butyloxycarbonyl-L-ornithinyl)thiazolidine (80mg, 0.26mmol) was dissolved in CH₂Cl₂ /DMF (9:1, 20mL). To this solution at 0°C was added 1-hydroxybenzotriazole hydrate (80mg, 0.6mmol), water-soluble carbodiimide (65mg, 0.32mmol), niflumic acid (82mg, 0.29mmol) and N-methylmorpholine (100mg, 1.0mmol). After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (70mL). The solution was washed with 0.3M KHSO₄ (1 x 20mL), sat. NaHCO₃ (1 x 20mL), water (1 x 20mL) and brine (1 x 20mL), dried (Na₂SO₄) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 75% ethyl acetate, 25% pet. ether) to give a yellow oil identified as 3-[N^α-*tert*-butyloxycarbonyl-N^ω-(2-(3'-trifluoromethylanilino)pyridyl-3-carbonyl)-L-ornithinyl]thiazolidine (60mg, 0.12mmol, 45%).

D. (2S)-1-[N^ω-(2-(3'-Trifluoromethylanilino)pyridyl-3-carbonyl)-L-ornithyl]thiazolidine dihydrochloride

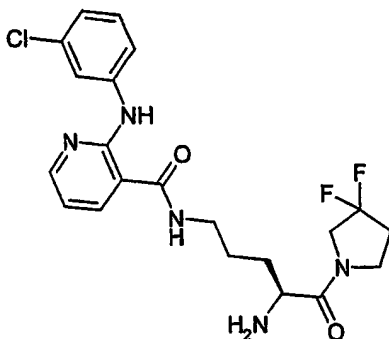
3-[N^α-*tert*-Butyloxycarbonyl-N^ω-(2-(3'-trifluoromethylanilino)pyridyl-3-carbonyl)-L-ornithinyl]thiazolidine (54mg, 0.10mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a pale brown solid identified as (2S)-1-[N^ω-(2-(3'-trifluoromethylanilino)pyridyl-3-carbonyl)-L-ornithyl]thiazolidine dihydrochloride (47mg, 0.10mmol, 100%).

$[M+H]^+ = 468.0$

^1H NMR (CD_3OD): δ 1.77-1.82 (2H, m), 1.84-2.00 (2H, m), 3.03-3.15 (4H, m), 3.41-3.51 (2H, m), 3.65-3.71 (2H, m), 3.80-3.87 (1H, m), 4.46-4.49 (2H, m), 4.65-4.72 (2H, m), 7.06-7.11 (1H, m), 7.61-7.11 (3H, m), 7.95 (1H, s), 8.09 (1H, d, $J=4.7\text{Hz}$), 8.49 (1H, d, $J=4.2\text{Hz}$) ppm.

EXAMPLE 13

3,3-Difluoro-1-[N^α -(2-(3'-chloroanilino)pyridyl-3-carbonyl)-L-ornithyl]pyrrolidine dihydrochloride



A. 1-[N^α -(*tert*-Butyloxycarbonyl)-L-ornithyl]-3,3-difluoropyrrolidine

1-[N^α -(*tert*-Butyloxycarbonyl)-L-ornithyl]-3,3-difluoropyrrolidine was prepared as described for the lysine derivative in Example 9.

B. 3-Chloroanilinonicotinic acid

3-Chloroaniline was dissolved in xylene. 2-Aminonicotinic acid was added. The reaction mixture was heated at 150°C for 18 hours after which time the reaction mixture was diluted with ethyl acetate giving an off-white solid identified as 3-chloroanilinonicotinic acid.

C. 3,3-Difluoro-[N^α -(*tert*-butyloxycarbonyl)- N^β -(2-(3'-chloroanilino)pyridyl-3-carbonyl)-L-ornithyl]pyrrolidine

1-[N^α -(*tert*-Butyloxycarbonyl)-L-ornithyl]-3,3-difluoropyrrolidine was dissolved in CH_2Cl_2 /DMF (9:1, 20mL). To this solution at 0°C was added 1-hydroxybenzotriazole hydrate, water-soluble carbodiimide, 3-chloroanilinonicotinic acid and N-methylmorpholine.

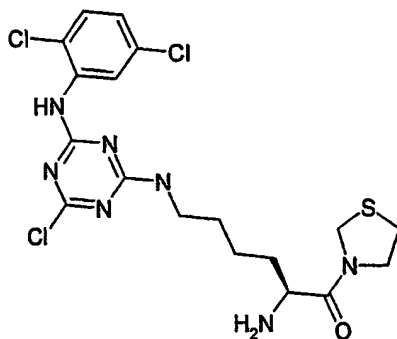
After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (70mL). The solution was washed with 0.3M KHSO₄ (1 x 20mL), sat. NaHCO₃ (1 x 20mL), water (1 x 20mL) and brine (1 x 20mL), dried (Na₂SO₄) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 75% ethyl acetate, 25% pet. ether) to give a yellow oil identified as 3,3-difluoro-[N^α-*tert*-butyloxycarbonyl-N^ω-(2-(3'-chloroanilino)pyridyl-3-carbonyl)]-L-ornithinyl)pyrrolidine.

D. 3,3-Difluoro-1-[N^o-(2-(3'-chloroanilino)pyridyl-3-carbonyl)-L-ornithyl]pyrrolidine dihydrochloride

3,3-Difluoro-[N^α-*tert*-butyloxycarbonyl-N^β-(2-(3'-chloroanilino)pyridyl-3-carbonyl)]-L-ornithinyl)pyrrolidine was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a pale brown solid identified as 3,3-difluoro-1-[N^β-(2-(3'-chloroanilino)pyridyl-3-carbonyl)-L-ornithyl]pyrrolidine dihydrochloride.

EXAMPLE 14

3-[N^o-6-Chloro-4-(2',5'-dichloroanilino)-1,3,5-triazinyl]-L-lysiny]thiazolidine dihydrochloride



A. 4,6-Dichloro-2-(2',5'-dichloroanilino)-1,3,5-triazine

Cyanuric chloride (1.844g, 10mmol) was dissolved in acetonitrile (20mL). The solution was cooled to -20°C . A solution of 2,5-dichloroaniline (1.62g, 10mmol) and triethylamine (1.0g, 10mmol) was slowly added. After 1 hour at -20°C the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (150mL). The

solution was washed with water (1 x 50mL) and brine (1 x 50mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was recrystallised from ethyl acetate/ hexane to give an off white solid identified as 4,6-dichloro-2-(2',5'-dichloroanilino)-1,3,5-triazine (1.86mg, 6.0mmol, 60%).

B. 3-[N^α-*tert*-Butyloxycarbonyl-N^ω-6-chloro-4-(2',5'-dichloroanilino)-1,3,5-triazinyl]-L-lysiny]thiazolidine

3-(N^α-(*tert*-Butyloxycarbonyl)-L-lysiny]thiazolidine (800mg, 2.58mmol) was dissolved in dichloromethane (30mL). To this solution was added 4,6-dichloro-2-(2',5'-dichloroanilino)-1,3,5-triazine (810mg, 2.6mmol) and triethylamine (300mg, 3.0mmol). After 2 hours at room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (150mL). This solution was washed with water (2 x 30mL) and brine (1 x 30mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography (eluant: 60% ethyl acetate, 40% pet. ether) to give a white solid identified as 3-[N^α-*tert*-butyloxycarbonyl-N^ω-6-chloro-4-(2',5'-dichloroanilino)-1,3,5-triazinyl]-L-lysiny]thiazolidine (1.33g, 2.23mmol, 86%).

C. 3-[N^ω-6-Chloro-4-(2',5'-dichloroanilino)-1,3,5-triazinyl]-L-lysiny]thiazolidine dihydrochloride

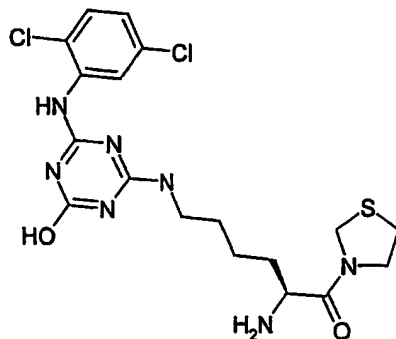
3-[N^α-*tert*-Butyloxycarbonyl-N^ω-6-chloro-4-(2',5'-dichloroanilino)-1,3,5-triazinyl]-L-lysiny]thiazolidine (59mg, 0.10mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 3-[N^ω-6-chloro-4-(2',5'-dichloroanilino)-1,3,5-triazinyl]-L-lysiny]thiazolidine dihydrochloride (55mg, 0.098mmol, 98%).

$[\text{M}+\text{H}]^+ = 492.2, 494.4$

^1H NMR (CD_3OD): δ 1.46-1.51 (2H,m), 1.65-1.67 (2H,m), 1.80-1.96 (2H,m), 3.05-3.14 (2H,m), 3.38-3.42 (2H,m), 3.55-3.75 (4H,m), 4.31-4.36 (2H,m), 4.40-4.52 (1H,m), 4.63-4.95 (2H,m), 7.15-7.18 (1H,m), 7.40-7.45 (1H,m), 8.15-8.25 (1H,m) ppm.

EXAMPLE 15

3-[N^o-4-(2',5'-Dichloroanilino)-6-hydroxy-1,3,5-triazinyl]-L-lysiny]thiazolidine bis(trifluoroacetate)

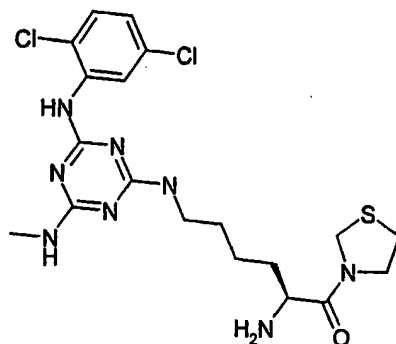


A. 3-[N^o-4-(2',5'-Dichloroanilino)-6-hydroxy-1,3,5-triazinyl]-L-lysiny]thiazolidine bis(trifluoroacetate)

3-[N^o-*tert*-Butyloxycarbonyl-N^o-6-chloro-4-(2',5'-dichloroanilino)-1,3,5-triazinyl]-L-ornithiny]thiazolidine (54mg, 0.09mmol) was dissolved in trifluoroacetic acid (20mL) and water (2mL). After 2 hours at 70 °C the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 3-[N^o-4-(2',5'-dichloroanilino)-6-hydroxy-1,3,5-triazinyl]-L-lysiny]thiazolidine bis(trifluoroacetate) (63mg, 0.089mmol, 97%).

[M+H]⁺ = 472.1, 474.2

¹H NMR (CD₃OD): δ 1.42-1.47 (2H,m), 1.62-1.67 (2H,m), 1.82-1.89 (2H,m), 3.04-3.16 (4H,m), 3.70-3.75 (2H,m), 3.84-3.91 (1H,m), 4.25-4.32 (2H,m), 4.45-4.54 (2H,m), 4.64-4.70 (2H,m), 7.05-7.15 (1H,m), 7.34-7.38 (1H,m), 7.49-7.55 (1H,m), 7.80-7.92 (1H,m) ppm.

EXAMPLE 16**3-[N^o-4-(2',5'-Dichloroanilino)-6-methylamino-1,3,5-triazinyl]-L-lysiny]thiazolidine dihydrochloride****A. 3-[N^o-*tert*-Butyloxycarbonyl-N^o-4-(2',5'-dichloroanilino)-6-dimethylamino-1,3,5-triazinyl]-L-lysiny]thiazolidine**

3-[N^o-*tert*-Butyloxycarbonyl-N^o-3-chloro-5-(2',5'-dichloroanilino)-2,4,6-triazinyl]-L-ornithiny]thiazolidine (120mg, 0.20mmol) was dissolved in 1M dimethylamine in tetrahydrofuran (25mL). After 18 hours at room temperature the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (eluant: 70% ethyl acetate, 30% pet. ether) to give a white solid identified as 3-[N^o-*tert*-butyloxycarbonyl-N^o-4-(2',5'-dichloroanilino)-6-dimethylamino-1,3,5-triazinyl]-L-lysiny]thiazolidine (110mg, 0.18mmol, 90%).

B. 3-[N^o-4-(2',5'-Dichloroanilino)-6-dimethylamino-1,3,5-triazinyl]-L-lysiny]-thiazolidine dihydrochloride

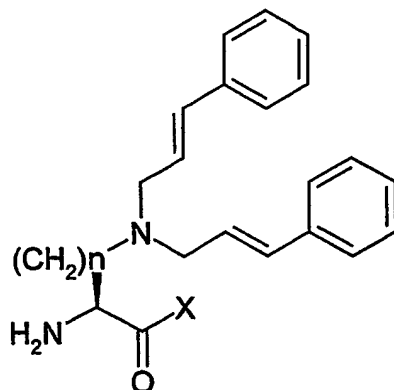
3-[N^o-*tert*-Butyloxycarbonyl-N^o-4-(2',5'-dichloroanilino)-6-dimethylamino-1,3,5-triazinyl]-L-lysiny]thiazolidine (110mg, 0.18mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 3-[N^o-4-(2',5'-dichloroanilino)-6-dimethylamino-1,3,5-triazinyl]-L-lysiny]thiazolidine dihydrochloride (105mg, 0.18mmol, 100%).

[M+H]⁺ = 499.1, 501.1

^1H NMR (CD_3OD): δ 1.52-1.55 (2H,m), 1.69-1.71 (2H,m), 1.90-1.98 (2H,m), 3.13-3.22 (8H,m), 3.48-3.62 (2H,m), 3.65-3.69 (4H,m), 4.37-4.39 (2H,m), 4.46-4.49 (1H,m), 4.57-4.77 (2H,m), 7.20-7.22 (1H,m), 7.45-7.50 (1H,m), 8.09-8.12 (1H,m) ppm.

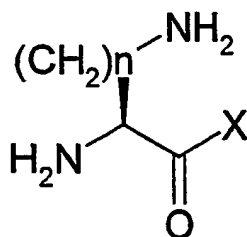
The following compounds were prepared by analogous methods.

TABLE 1



Example No	n	X	Example No	n	X
17	3		22	3	
			23	4	
18	3		24	3	
19	4		25	4	
20	3		26	3	
21	4		27	4	

TABLE 2





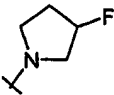
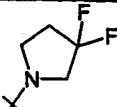
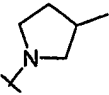
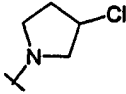
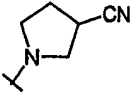



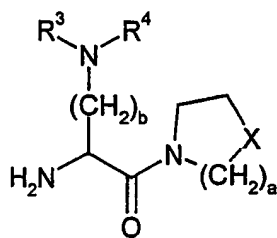
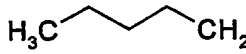
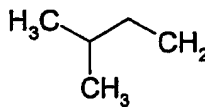
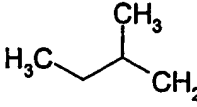
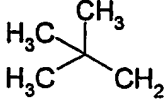
Example No	n	X	Example No	n	X
28	2		41	2	
29	2		42	2	
30	3		43	3	
31	4		45	4	
32	2		46	2	
33	3		47	3	
34	4		48	4	
35	2		49	2	
36	3		50	2	
37	4			3	
38	2			4	
39	3	51	3		
40	4	52	4		

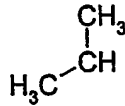
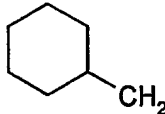
TABLE 3

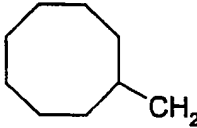
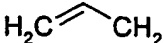


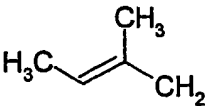
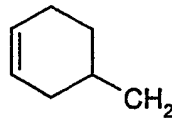
Ex No	a	b	X	R ³	R ⁴
53	1	3	S	H	
54	1	4		H	
55	1	3	CH ₂	H	
56	1	4		H	
57	1	3	CF ₂	H	
58	1	4		H	
59	1	4	S	CH ₃	
60	1	4		CH(CH ₃) ₂	
61	1	4	CH ₂	CH ₃	
62	1	4		CH(CH ₃) ₂	

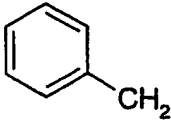
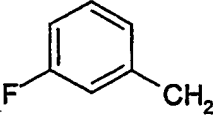
Ex No	a	b	X	R ³	R ⁴
63	1	3	S	CH(CH ₃) ₂	
64	1	3	CH ₂	CH(CH ₃) ₂	
65	2	3	S	H	
66	2	4		H	
67	2	3	CH ₂	H	
68	2	4		H	
69	1	3	S	H	
70	1	4		H	
71	1	3	CH ₂	H	
72	1	4		H	
73	1	3	CF ₂	H	
74	1	4		H	
75	1	4	S	CH ₃	
76	1	4		CH(CH ₃) ₂	
77	1	4	CH ₂	CH ₃	
78	1	4		CH(CH ₃) ₂	
79	1	3	S	CH(CH ₃) ₂	
80	1	3	CH ₂	CH(CH ₃) ₂	
81	2	3	S	H	
82	2	4		H	
83	2	3	CH ₂	H	
84	2	4		H	
85	1	3	S	H	
86	1	4		H	
87	1	3	CH ₂	H	
88	1	4		H	
89	1	3	CF ₂	H	
90	1	4		H	
91	1	4	S	CH ₃	
92	1	4		CH(CH ₃) ₂	
93	1	4	CH ₂	CH ₃	
94	1	4		CH(CH ₃) ₂	
95	1	3	S	CH(CH ₃) ₂	

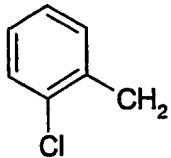
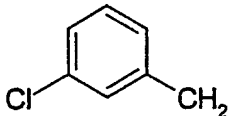
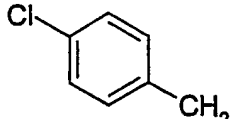
Ex No	a	b	X	R ³	R ⁴
96	1	3	CH ₂	CH(CH ₃) ₂	
97	2	3	S	H	
98	2	4		H	
99	2	3	CH ₂	H	
100	2	4		H	
101	1	3	S	H	
102	1	4		H	
103	1	3	CH ₂	H	
104	1	4		H	
105	1	3	CF ₂	H	
106	1	4	S	CH ₃	
107	1	4		CH(CH ₃) ₂	
108	1	4	CH ₂	CH ₃	
109	1	4		CH(CH ₃) ₂	
110	1	3	S	CH(CH ₃) ₂	
111	1	3	CH ₂	CH(CH ₃) ₂	
112	2	3	S	H	
113	2	4		H	
114	2	3	CH ₂	H	
115	2	4		H	
116	1	3	S	H	
117	1	4		H	
118	1	3	CH ₂	H	
119	1	4		H	
120	1	3	CF ₂	H	
121	1	4		H	
122	1	4	S	CH ₃	
123	1	4		CH(CH ₃) ₂	
124	1	4	CH ₂	CH ₃	
125	1	4		CH(CH ₃) ₂	
126	1	3	S	CH(CH ₃) ₂	
127	1	3	CH ₂	CH(CH ₃) ₂	
128	2	3	S	H	

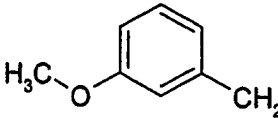
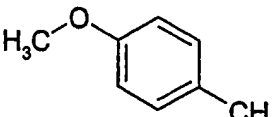
Ex No	a	b	X	R ³	R ⁴
129	2	4		H	
130	2	3	CH ₂	H	
131	2	4		H	
132	1	3	S	H	
133	1	4		H	
134	1	3	CH ₂	H	
135	1	4		H	
136	1	3	CF ₂	H	
137	1	4		H	
138	1	4	S	CH ₃	
139	1	4		CH(CH ₃) ₂	
140	1	4	CH ₂	CH ₃	
141	1	4		CH(CH ₃) ₂	
142	1	3	S	CH(CH ₃) ₂	
143	1	3	CH ₂	CH(CH ₃) ₂	
144	2	3	S	H	
145	2	4		H	
146	2	3	CH ₂	H	
147	2	4		H	
148	1	3	S		
149	1	4			
150	1	4	CH ₂		
151	1	3	CF ₂		
152	1	4			
153	1	4	S	CH ₃	
154	1	4		CH(CH ₃) ₂	
155	1	4	CH ₂	CH ₃	
156	1	4		CH(CH ₃) ₂	
157	1	3	S	CH(CH ₃) ₂	
158	1	3	CH ₂	CH(CH ₃) ₂	
159	2	3	S	H	
160	2	4		H	
161	2	3	CH ₂	H	

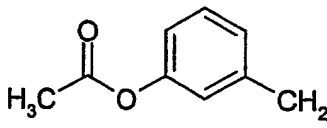
Ex No	a	b	X	R ³	R ⁴
162	2	4		H	
163	1	3	S	H	
164	1	4		H	
165	1	3	CH ₂	H	
166	1	4		H	
167	1	3	CF ₂	H	
168	1	4		H	
169	1	4	S	CH ₃	
170	1	4		CH(CH ₃) ₂	
171	1	4	CH ₂	CH ₃	
172	1	4		CH(CH ₃) ₂	
173	1	3	S	CH(CH ₃) ₂	
174	1	3	CH ₂	CH(CH ₃) ₂	
175	2	3	S	H	
176	2	4		H	
177	2	3	CH ₂	H	
178	2	4		H	
179	1	3	S	H	
180	1	4		H	
181	1	3	CH ₂	H	
182	1	4		H	
183	1	3	CF ₂	H	
184	1	4		H	
185	1	4	S	CH ₃	
186	1	4		CH(CH ₃) ₂	
187	1	4	CH ₂	CH ₃	
188	1	4		CH(CH ₃) ₂	
189	1	3	S	CH(CH ₃) ₂	
190	1	3	CH ₂	CH(CH ₃) ₂	
191	2	3	S	H	
192	2	4		H	
193	2	3	CH ₂	H	
194	2	4		H	

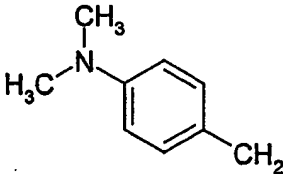
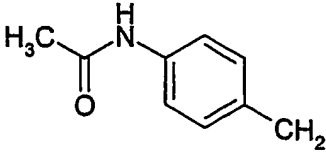
Ex No	a	b	X	R ³	R ⁴
195	1	3	S	H	
196	1	4		H	
197	1	3	CH ₂	H	
198	1	4		H	
199	1	3	CF ₂	H	
200	1	4		H	
201	1	4	S	CH ₃	
202	1	4		CH(CH ₃) ₂	
203	1	4	CH ₂	CH ₃	
204	1	4		CH(CH ₃) ₂	
205	1	3	S	CH(CH ₃) ₂	
206	1	3	CH ₂	CH(CH ₃) ₂	
207	2	3	S	H	
208	2	4		H	
209	2	3	CH ₂	H	
210	2	4		H	
211	1	3	S	H	
212	1	4		H	
213	1	3	CH ₂	H	
214	1	4		H	
215	1	3	CF ₂	H	
216	1	4		H	
217	1	4	S	CH ₃	
218	1	4		CH(CH ₃) ₂	
219	1	4	CH ₂	CH ₃	
220	1	4		CH(CH ₃) ₂	
221	1	3	S	CH(CH ₃) ₂	
222	1	3	CH ₂	CH(CH ₃) ₂	
223	2	3	S	H	
224	2	3	CH ₂	H	
225	2	4		H	
226	1	3	S	H	
227	1	4		H	

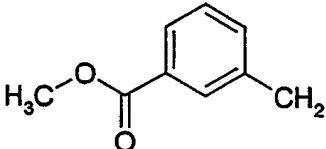
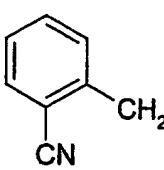
Ex No	a	b	X	R ³	R ⁴
228	1	3	CH ₂	H	
229	1	4		H	
230	1	3	CF ₂	H	
231	1	4		H	
232	1	4	S	CH ₃	
233	1	4		CH(CH ₃) ₂	
234	1	4	CH ₂	CH ₃	
235	1	4		CH(CH ₃) ₂	
236	1	3	S	CH(CH ₃) ₂	
237	1	3	CH ₂	CH(CH ₃) ₂	
238	2	3	S	H	
239	2	4		H	
240	2	3	CH ₂	H	
241	2	4		H	
242	1	3	S	H	
243	1	4		H	
244	1	3	CH ₂	H	
245	1	4		H	
246	1	3	CF ₂	H	
247	1	4		H	
248	1	4	S	CH ₃	
249	1	4		CH(CH ₃) ₂	
250	1	4	CH ₂	CH ₃	
251	1	4		CH(CH ₃) ₂	
252	1	3	S	CH(CH ₃) ₂	
253	1	3	CH ₂	CH(CH ₃) ₂	
254	2	3	S	H	
255	2	4		H	
256	2	3	CH ₂	H	
257	2	4		H	
258	1	3	S	H	
259	1	4		H	
260	1	3	CH ₂	H	

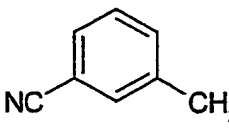
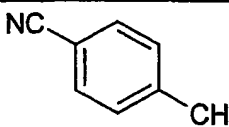
Ex No	a	b	X	R ³	R ⁴
261	1	4		H	
262	1	3	CF ₂	H	
263	1	4		H	
264	1	4	S	CH ₃	
265	1	4		CH(CH ₃) ₂	
266	1	4	CH ₂	CH ₃	
267	1	4		CH(CH ₃) ₂	
268	1	3	S	CH(CH ₃) ₂	
269	1	3	CH ₂	CH(CH ₃) ₂	
270	2	3	S	H	
271	2	4		H	
272	2	3	CH ₂	H	
273	2	4		H	
274	1	3	S	H	
275	1	4		H	
276	1	3	CH ₂	H	
277	1	4		H	
278	1	3	CF ₂	H	
279	1	4		H	
280	1	4	S	CH ₃	
281	1	4		CH(CH ₃) ₂	
282	1	4	CH ₂	CH ₃	
283	1	4		CH(CH ₃) ₂	
284	1	3	S	CH(CH ₃) ₂	
285	1	3	CH ₂	CH(CH ₃) ₂	
286	2	3	S	H	
287	2	4		H	
288	2	3	CH ₂	H	
289	2	4		H	
290	1	3	S	H	
291	1	4		H	
292	1	3	CH ₂	H	
293	1	4		H	

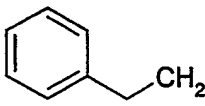
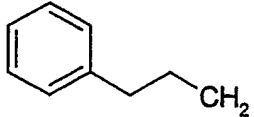
Ex No	a	b	X	R ³	R ⁴
294	1	3	CF ₂	H	
295	1	4		H	
296	1	4	S	CH ₃	
297	1	4		CH(CH ₃) ₂	
298	1	4	CH ₂	CH ₃	
299	1	4		CH(CH ₃) ₂	
300	1	3	S	CH(CH ₃) ₂	
301	1	3	CH ₂	CH(CH ₃) ₂	
302	2	3	S	H	
303	2	4		H	
304	2	3	CH ₂	H	
305	2	4		H	
306	1	3	S	H	
307	1	4		H	
308	1	3	CH ₂	H	
309	1	4		H	
310	1	3	CF ₂	H	
311	1	4		H	
312	1	4	S	CH ₃	
313	1	4		CH(CH ₃) ₂	
314	1	4	CH ₂	CH ₃	
315	1	4		CH(CH ₃) ₂	
316	1	3	S	CH(CH ₃) ₂	
317	1	3	CH ₂	CH(CH ₃) ₂	
318	2	3	S	H	
319	2	4		H	
320	2	3	CH ₂	H	
321	2	4		H	
322	1	3	S	H	
323	1	4		H	
324	1	3	CH ₂	H	
325	1	4		H	
326	1	3	CF ₂	H	

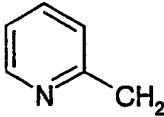
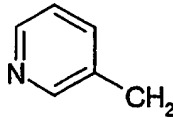
Ex No	a	b	X	R ³	R ⁴
327	1	4		H	
328	1	4	S	CH ₃	
329	1	4		CH(CH ₃) ₂	
330	1	4	CH ₂	CH ₃	
331	1	4		CH(CH ₃) ₂	
332	1	3	S	CH(CH ₃) ₂	
333	1	3	CH ₂	CH(CH ₃) ₂	
334	2	3	S	H	
335	2	4		H	
336	2	3	CH ₂	H	
337	2	4		H	
338	1	3	S	H	
339	1	4		H	
340	1	3	CH ₂	H	
341	1	4		H	
342	1	3	CF ₂	H	
343	1	4		H	
344	1	4	S	CH ₃	
345	1	4		CH(CH ₃) ₂	
346	1	4	CH ₂	CH ₃	
347	1	4		CH(CH ₃) ₂	
348	1	3	S	CH(CH ₃) ₂	
349	1	3	CH ₂	CH(CH ₃) ₂	
350	2	3	S	H	
351	2	4		H	
352	2	3	CH ₂	H	
353	2	4		H	
354	1	3	S	H	
355	1	4		H	
356	1	3	CH ₂	H	
357	1	4		H	
358	1	3	CF ₂	H	
359	1	4		H	

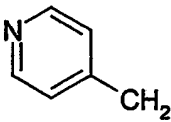
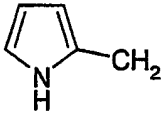
Ex No	a	b	X	R ³	R ⁴
360	1	4	S	CH ₃	
361	1	4		CH(CH ₃) ₂	
362	1	4	CH ₂	CH ₃	
363	1	4		CH(CH ₃) ₂	
364	1	3	S	CH(CH ₃) ₂	
365	1	3	CH ₂	CH(CH ₃) ₂	
366	2	3	S	H	
367	2	4		H	
368	2	3	CH ₂	H	
369	2	4		H	
370	1	3	S	H	
371	1	4		H	
372	1	3	CH ₂	H	
373	1	4		H	
374	1	3	CF ₂	H	
375	1	4		H	
376	1	4	S	CH ₃	
377	1	4		CH(CH ₃) ₂	
378	1	4	CH ₂	CH ₃	
379	1	4		CH(CH ₃) ₂	
380	1	3	S	CH(CH ₃) ₂	
381	1	3	CH ₂	CH(CH ₃) ₂	
382	2	3	S	H	
383	2	4		H	
384	2	3	CH ₂	H	
385	2	4		H	
386	1	3	S	H	
387	1	4		H	
388	1	3	CH ₂	H	
389	1	4		H	
390	1	3	CF ₂	H	
391	1	4		H	
392	1	4	S	CH ₃	

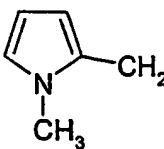
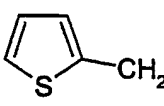
Ex No	a	b	X	R ³	R ⁴
393	1	4		CH(CH ₃) ₂	
394	1	4	CH ₂	CH ₃	
395	1	4		CH(CH ₃) ₂	
396	1	3	S	CH(CH ₃) ₂	
397	1	3	CH ₂	CH(CH ₃) ₂	
398	2	3	S	H	
399	2	4		H	
400	2	3	CH ₂	H	
401	2	4		H	
402	1	3	S	H	
403	1	4		H	
404	1	3	CH ₂	H	
405	1	4		H	
406	1	3	CF ₂	H	
407	1	4		H	
408	1	4	S	CH ₃	
409	1	4		CH(CH ₃) ₂	
410	1	4	CH ₂	CH ₃	
411	1	4		CH(CH ₃) ₂	
412	1	3	S	CH(CH ₃) ₂	
413	1	3	CH ₂	CH(CH ₃) ₂	
414	2	3	S	H	
415	2	4		H	
416	2	3	CH ₂	H	
417	2	4		H	
418	1	3	S	H	
419	1	4		H	
420	1	3	CH ₂	H	
421	1	4		H	
422	1	3	CF ₂	H	
423	1	4		H	
424	1	4	S	CH ₃	
425	1	4		CH(CH ₃) ₂	

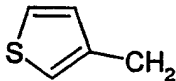
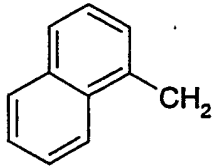
Ex No	a	b	X	R ³	R ⁴
426	1	4	CH ₂	CH ₃	
427	1	4		CH(CH ₃) ₂	
428	1	3	S	CH(CH ₃) ₂	
429	1	3	CH ₂	CH(CH ₃) ₂	
450	2	3	S	H	
451	2	4		H	
452	2	3	CH ₂	H	
453	2	4		H	
454	1	3	S	H	
455	1	4		H	
456	1	3	CH ₂	H	
457	1	4		H	
458	1	3	CF ₂	H	
459	1	4		H	
460	1	4	S	CH ₃	
461	1	4		CH(CH ₃) ₂	
462	1	4	CH ₂	CH ₃	
463	1	4		CH(CH ₃) ₂	
464	1	3	S	CH(CH ₃) ₂	
465	1	3	CH ₂	CH(CH ₃) ₂	
466	2	3	S	H	
467	2	4		H	
468	2	3	CH ₂	H	
469	2	4		H	
470	1	3	S	H	
471	1	4		H	
472	1	3	CH ₂	H	
473	1	4		H	
474	1	3	CF ₂	H	
475	1	4		H	
476	1	4	S	CH ₃	
477	1	4		CH(CH ₃) ₂	
478	1	4	CH ₂	CH ₃	

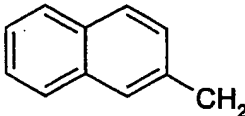
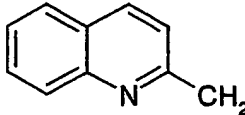
Ex No	a	b	X	R ³	R ⁴
479	1	4		CH(CH ₃) ₂	
480	1	3	S	CH(CH ₃) ₂	
481	1	3	CH ₂	CH(CH ₃) ₂	
482	2	3	S	H	
483	2	4		H	
484	2	3	CH ₂	H	
485	2	4		H	
486	1	3	S	H	
487	1	4		H	
488	1	3	CH ₂	H	
489	1	4		H	
490	1	3	CF ₂	H	
491	1	4		H	
492	1	4	S	CH ₃	
493	1	4		CH(CH ₃) ₂	
494	1	4	CH ₂	CH ₃	
495	1	4		CH(CH ₃) ₂	
496	1	3	S	CH(CH ₃) ₂	
497	1	3	CH ₂	CH(CH ₃) ₂	
498	2	3	S	H	
499	2	4		H	
500	2	3	CH ₂	H	
501	2	4		H	
502	1	3	S	H	
503	1	4		H	
504	1	3	CH ₂	H	
505	1	4		H	
506	1	3	CF ₂	H	
507	1	4		H	
508	1	4	S	CH ₃	
509	1	4		CH(CH ₃) ₂	
510	1	4	CH ₂	CH ₃	
511	1	4		CH(CH ₃) ₂	

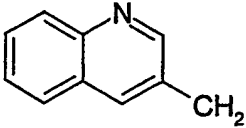
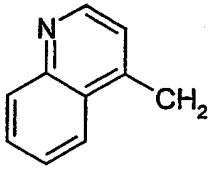
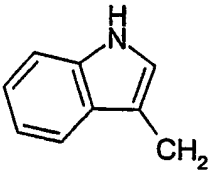
Ex No	a	b	X	R ³	R ⁴
512	1	3	S	CH(CH ₃) ₂	
513	1	3	CH ₂	CH(CH ₃) ₂	
514	2	3	S	H	
515	2	4		H	
516	2	3	CH ₂	H	
517	2	4		H	
518	1	3	S	H	
519	1	4		H	
520	1	3	CH ₂	H	
521	1	4		H	
522	1	3	CF ₂	H	
523	1	4		H	
524	1	4	S	CH ₃	
525	1	4		CH(CH ₃) ₂	
526	1	4	CH ₂	CH ₃	
527	1	4		CH(CH ₃) ₂	
528	1	3	S	CH(CH ₃) ₂	
529	1	3	CH ₂	CH(CH ₃) ₂	
530	2	3	S	H	
531	2	4		H	
532	2	3	CH ₂	H	
533	2	4		H	
534	1	3	S	H	
535	1	4		H	
536	1	3	CH ₂	H	
537	1	4		H	
538	1	3	CF ₂	H	
539	1	4		H	
540	1	4	S	CH ₃	
541	1	4		CH(CH ₃) ₂	
542	1	4	CH ₂	CH ₃	
543	1	4		CH(CH ₃) ₂	
544	1	3	S	CH(CH ₃) ₂	

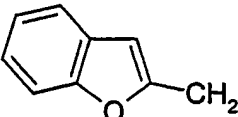
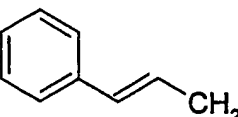
Ex No	a	b	X	R ³	R ⁴
545	1	3	CH ₂	CH(CH ₃) ₂	
546	2	3	S	H	
547	2	4		H	
548	2	3	CH ₂	H	
549	2	4		H	
550	1	3	S	H	
551	1	4		H	
552	1	3	CH ₂	H	
553	1	4		H	
554	1	3	CF ₂	H	
555	1	4		H	
556	1	4	S	CH ₃	
557	1	4		CH(CH ₃) ₂	
558	1	4	CH ₂	CH ₃	
559	1	4		CH(CH ₃) ₂	
560	1	3	S	CH(CH ₃) ₂	
561	1	3	CH ₂	CH(CH ₃) ₂	
562	2	3	S	H	
563	2	4		H	
564	2	3	CH ₂	H	
565	2	4		H	
566	1	3	S	H	
567	1	4		H	
568	1	3	CH ₂	H	
569	1	4		H	
570	1	3	CF ₂	H	
571	1	4		H	
572	1	4	S	CH ₃	
573	1	4		CH(CH ₃) ₂	
574	1	4	CH ₂	CH ₃	
575	1	4		CH(CH ₃) ₂	
576	1	3	S	CH(CH ₃) ₂	
577	1	3	CH ₂	CH(CH ₃) ₂	

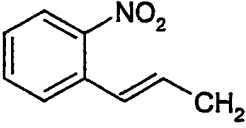

Ex No	a	b	X	R ³	R ⁴
578	2	3	S	H	
579	2	4		H	
580	2	3	CH ₂	H	
581	2	4		H	
582	1	3	S	H	
583	1	4		H	
584	1	3	CH ₂	H	
585	1	4		H	
586	1	3	CF ₂	H	
587	1	4		H	
588	1	4	S	CH ₃	
589	1	4		CH(CH ₃) ₂	
590	1	4	CH ₂	CH ₃	
591	1	4		CH(CH ₃) ₂	
592	1	3	S	CH(CH ₃) ₂	
593	1	3	CH ₂	CH(CH ₃) ₂	
594	2	3	S	H	
595	2	4		H	
596	2	3	CH ₂	H	
597	2	4		H	
598	1	3	S	H	
599	1	4		H	
600	1	3	CH ₂	H	
601	1	4		H	
602	1	3	CF ₂	H	
603	1	4		H	
604	1	4	S	CH ₃	
605	1	4		CH(CH ₃) ₂	
606	1	4	CH ₂	CH ₃	
607	1	4		CH(CH ₃) ₂	
608	1	3	S	CH(CH ₃) ₂	
609	1	3	CH ₂	CH(CH ₃) ₂	
610	2	3	S	H	

Ex No	a	b	X	R ³	R ⁴
611	2	4		H	
612	2	3	CH ₂	H	
613	2	4		H	
614	1	3	S	H	
615	1	4		H	
616	1	3	CH ₂	H	
617	1	4		H	
618	1	3	CF ₂	H	
619	1	4		H	
620	1	4	S	CH ₃	
621	1	4		CH(CH ₃) ₂	
622	1	4	CH ₂	CH ₃	
623	1	4		CH(CH ₃) ₂	
624	1	3	S	CH(CH ₃) ₂	
625	1	3	CH ₂	CH(CH ₃) ₂	
626	2	3	S	H	
627	2	4		H	
628	2	3	CH ₂	H	
629	2	4		H	
630	1	3	S	H	
631	1	4		H	
632	1	3	CH ₂	H	
633	1	4		H	
634	1	3	CF ₂	H	
635	1	4		H	
636	1	4	S	CH ₃	
637	1	4		CH(CH ₃) ₂	
638	1	4	CH ₂	CH ₃	
639	1	4		CH(CH ₃) ₂	
640	1	3	S	CH(CH ₃) ₂	
641	1	3	CH ₂	CH(CH ₃) ₂	
642	2	3	S	H	
643	2	4		H	

Ex No	a	b	X	R ³	R ⁴
644	2	3	CH ₂	H	
645	2	4		H	
646	1	3	S	H	
647	1	4		H	
648	1	3	CH ₂	H	
649	1	4		H	
650	1	3	CF ₂	H	
651	1	4		H	
652	1	4	S	CH(CH ₃) ₂	
653	1	4	CH ₂	CH ₃	
654	1	4		CH(CH ₃) ₂	
655	1	3	S	CH(CH ₃) ₂	
656	1	3	CH ₂	CH(CH ₃) ₂	
657	2	3	S	H	
658	2	4		H	
659	2	3	CH ₂	H	
660	2	4		H	
661	1	3	S	H	
662	1	4		H	
663	1	3	CH ₂	H	
664	1	4		H	
665	1	3	CF ₂	H	
666	1	4		H	
667	1	4	S	CH ₃	
668	1	4		CH(CH ₃) ₂	
669	1	4	CH ₂	CH ₃	
670	1	4		CH(CH ₃) ₂	
671	1	3	S	CH(CH ₃) ₂	
672	1	3	CH ₂	CH(CH ₃) ₂	
673	2	3	S	H	
674	2	4		H	
675	2	3	CH ₂	H	
676	2	4		H	

Ex No	a	b	X	R ³	R ⁴
677	1	3	S	H	
678	1	4	CH ₂	H	
679	1	3	CF ₂	H	
680	1	4		H	
681	1	4	S	CH ₃	
682	1	4		CH(CH ₃) ₂	
683	1	4	CH ₂	CH ₃	
684	1	4		CH(CH ₃) ₂	
685	1	3	S	CH(CH ₃) ₂	
686	1	3	CH ₂	CH(CH ₃) ₂	
687	2	3	S	H	
688	2	4	CH ₂	H	
689	1	3	S	H	
690	1	4		H	
691	1	3	CH ₂	H	
692	1	4		H	
693	1	3	CF ₂	H	
694	1	4		H	
695	1	4	S	CH ₃	
696	1	4		CH(CH ₃) ₂	
697	1	4	CH ₂	CH ₃	
698	1	4		CH(CH ₃) ₂	
699	1	3	S	CH(CH ₃) ₂	
700	1	3	CH ₂	CH(CH ₃) ₂	
701	2	3	S	H	
702	2	4		H	
703	2	3	CH ₂	H	
704	2	4		H	
705	1	3	S	H	
706	1	4		H	
707	1	3	CH ₂	H	
708	1	4		H	
709	1	3	CF ₂	H	

Ex No	a	b	X	R ³	R ⁴
710	1	4		H	
711	1	4	S	CH ₃	
712	1	4		CH(CH ₃) ₂	
713	1	4	CH ₂	CH ₃	
714	1	4		CH(CH ₃) ₂	
715	1	3	S	CH(CH ₃) ₂	
716	1	3	CH ₂	CH(CH ₃) ₂	
717	2	3	S	H	
718	2	4		H	
719	2	3	CH ₂	H	
720	2	4		H	
721	1	3	S	H	
722	1	4		H	
723	1	3	CH ₂	H	
724	1	4		H	
725	1	3	CF ₂	H	
726	1	4		H	
727	1	4	S	CH ₃	
728	1	4		CH(CH ₃) ₂	
729	1	4	CH ₂	CH ₃	
730	1	4		CH(CH ₃) ₂	
731	1	3	S	CH(CH ₃) ₂	
732	1	3	CH ₂	CH(CH ₃) ₂	
733	2	3	S	H	
734	2	4		H	
735	2	3	CH ₂	H	
736	2	4		H	
737	1	3	S	H	
738	1	3	CH ₂	H	
739	1	4		H	
740	1	3	CF ₂	H	
741	1	4		H	
742	1	4	S	CH ₃	

Ex No	a	b	X	R ³	R ⁴
743	1	4		CH(CH ₃) ₂	
744	1	4	CH ₂	CH ₃	
745	1	4		CH(CH ₃) ₂	
746	1	3	S	CH(CH ₃) ₂	
747	1	3	CH ₂	CH(CH ₃) ₂	
748	2	3	S	H	
749	2	4		H	
750	2	3	CH ₂	H	
751	2	4		H	
752	1	3	S	H	
753	1	4		H	
754	1	3	CH ₂	H	
755	1	4		H	
756	1	3	CF ₂	H	
757	1	4		H	
758	1	4	S	CH ₃	
759	1	4		CH(CH ₃) ₂	
760	1	4	CH ₂	CH ₃	
761	1	4		CH(CH ₃) ₂	
762	1	3	S	CH(CH ₃) ₂	
763	1	3	CH ₂	CH(CH ₃) ₂	
764	2	3	S	H	
765	2	4		H	
766	2	3	CH ₂	H	
767	2	4		H	
768	1	3	S	H	
769	1	4		H	
770	1	3	CH ₂	H	
771	1	4		H	
772	1	3	CF ₂	H	
773	1	4		H	
774	1	4	S	CH ₃	
775	1	4		CH(CH ₃) ₂	

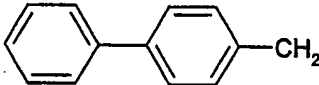
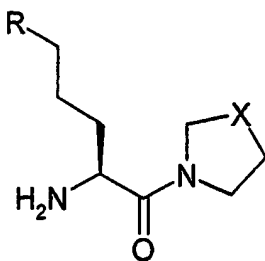
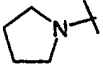
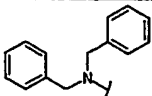
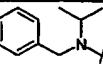
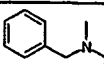
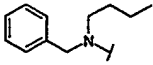
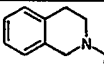
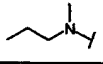
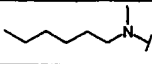
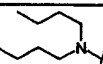
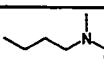
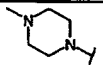


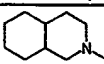
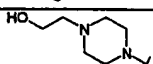
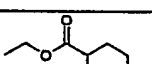
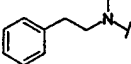
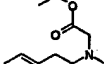
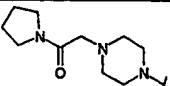
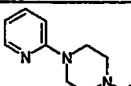
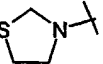
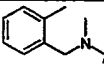
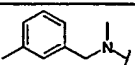
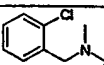
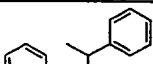
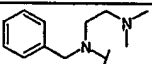
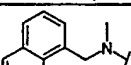
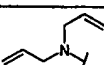

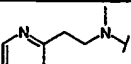
Ex No	a	b	X	R ³	R ⁴
776	1	4	CH ₂	CH ₃	
777	1	4		CH(CH ₃) ₂	
778	1	3	S	CH(CH ₃) ₂	
779	1	3	CH ₂	CH(CH ₃) ₂	
780	2	3	S	H	
781	2	4		H	
782	2	3	CH ₂	H	
783	2	4		H	
784	1	3	S	H	
785	1	4		H	
786	1	3	CH ₂	H	
787	1	4		H	
788	1	3	CF ₂	H	
789	1	4		H	
790	1	4	S	CH ₃	
791	1	4		CH(CH ₃) ₂	
792	1	4	CH ₂	CH ₃	
793	1	4		CH(CH ₃) ₂	
794	1	3	S	CH(CH ₃) ₂	
795	1	3	CH ₂	CH(CH ₃) ₂	
796	2	3	S	H	
797	2	4		H	
798	2	3	CH ₂	H	
799	2	4		H	

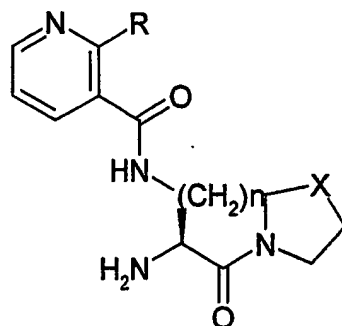
TABLE 4



Example No	X	R	Example No	X	R
800	S		841	S	
801	CH ₂		842	CH ₂	
802	S		843	S	
803	CH ₂		844	CH ₂	
804	S		845	S	
805	CH ₂		846	CH ₂	
806	S		847	S	
807	CH ₂		848	S	
808	S		849	CH ₂	
809	CH ₂				
810	S		850	S	
811	CH ₂		851	CH ₂	
812	S		852	S	
813	CH ₂		853	CH ₂	
814	S		854	S	
815	CH ₂		855	CH ₂	
816	S		856	S	
817	CH ₂		857	CH ₂	
818	S		858	S	
819	CH ₂		859	CH ₂	
820	S		860	S	
821	CH ₂		861	CH ₂	
822	S		862	S	
823	CH ₂		863	CH ₂	
824	S		864	S	
825	CH ₂		865	CH ₂	
826	S		866	S	
827	CH ₂		867	CH ₂	
828	CH ₂		868	S	
829	CH ₂		869	CH ₂	
830	S		870	S	
831	CH ₂		871	CH ₂	

832	S		872	S	
833	CH ₂		873	CH ₂	
834	S		874	S	
835	CH ₂		875	CH ₂	
836	S		876	S	
837	CH ₂		877	CH ₂	
838	S				
839	CH ₂				

TABLE 5



Example No	n	X	R	Example No	n	X	R
878	3	S		933	3	S	
879	4			934	4		
880	3	CH ₂		935	3	CH ₂	
881	4			936	4		
882	3	S		937	3	S	
883	4			938	4		
884	3	CH ₂		939	3	CH ₂	
885	4			940	4		
886	3	S		941	3	S	
887	4			942	4		
888	3	CH ₂		943	3	CH ₂	
889	4			944	4		

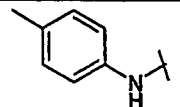
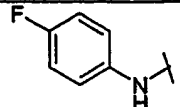
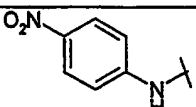
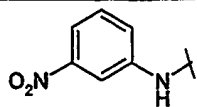
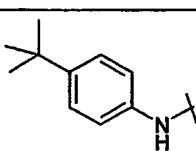
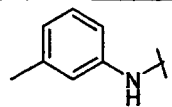
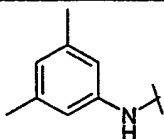
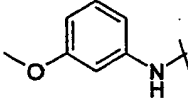
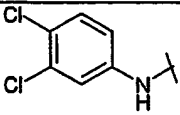
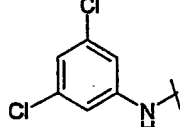
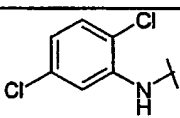
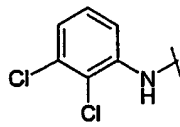
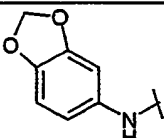
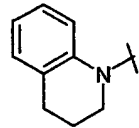
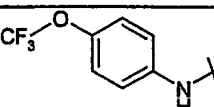
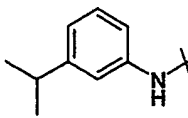
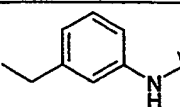
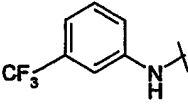
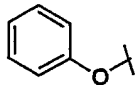
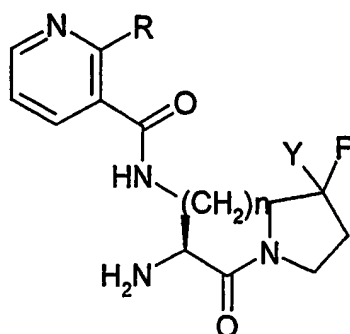
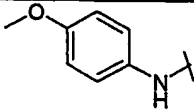
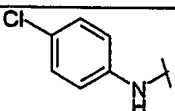
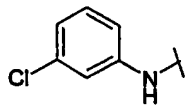
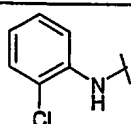
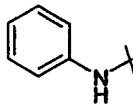
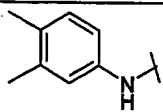
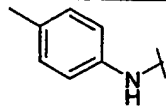
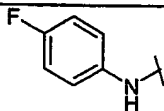
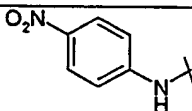
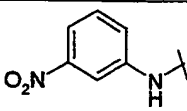
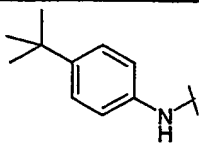
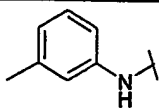
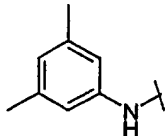
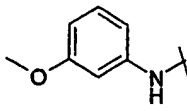
890	3	S		945	3	S	
891	4	CH ₂		946	4	CH ₂	
892	3						
893	4						
894	3	S		947	3	S	
895	4	CH ₂		948	4	CH ₂	
896	3			949	3		
897	4			950	4		
898	3	S		951	3	S	
899	4	CH ₂		952	4	CH ₂	
900	3			953	3		
901	4			954	4		
902	3	S		955	3	S	
903	4	CH ₂		956	4	CH ₂	
904	3			957	3		
905	4			958	4		
906	3	S		959	3	S	
907	4	CH ₂		960	4	CH ₂	
908	3			961	3		
909	4			962	4		
910	3	S		963	3	S	
911	4	CH ₂		964	4	CH ₂	
912	3			965	3		
913	4			966	4		
914	3	S		967	3	S	
915	4	CH ₂		968	4	CH ₂	
916	3			969	3		
917	4			970	4		
918	3	S		971	3	S	
919	4	CH ₂		972	4	CH ₂	
920	3			973	3		
0	4			974	4		
921	3	S		975	4	S	
922	4	CH ₂		976		CH ₂	
923	3			977	3		
924	4			978	4		
925	3	S		979	3	S	MeS
926	4	CH ₂		980	4	CH ₂	
927	3			981	3		
928	4			982	4		
929	3	S	Me	983	3	S	MeO
930	4	CH ₂		984	4	CH ₂	
931	3			985	3		
932	4			986	4		

TABLE 6



Example No	n	X	R	Example No	n	X	R
987	3	S		1044	3	S	
988	4			1045	4		
989	3	CH ₂		1046	3	CH ₂	
990	4			1047	4		
991	4	S		1048	3	S	
992	4			1049	4		
993	3	CH ₂		1050	3	CH ₂	
994	4			1051	4		
995	3	S		1052	3	S	
996	4			1053	4		
997	3	CH ₂		1054	3	CH ₂	
998	4			1055	4		
999	3	S		1056	3	S	
1000	4						
1001	3	CH ₂		1057	4	CH ₂	
1002	4						
1003	3	S		1058	3	S	
1004	4			1059	4		
1005	3	CH ₂		1060	3	CH ₂	
1006	4			1061	4		
1007	3	S		1062	3	S	
1008	4			1063	4		
1009	3	CH ₂		1064	3	CH ₂	
1010	4			1065	4		
1011	3	S		1066	3	S	
1012	4			1067	4		
1013	3	CH ₂		1068	3	CH ₂	
1014	4			1069	4		

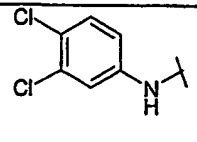
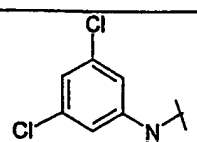
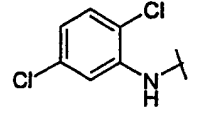
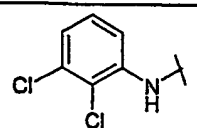
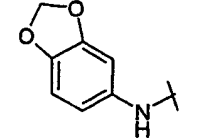
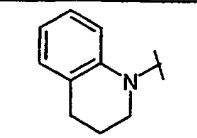
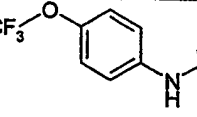
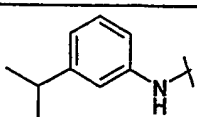
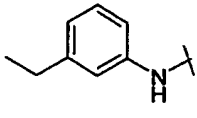
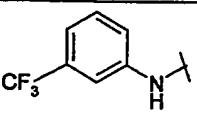
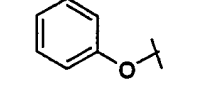
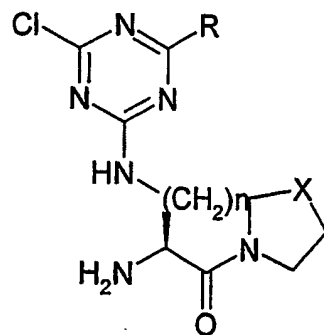
1015	3	S		1070	3	S			
1016	4			CH ₂	1071			4	CH ₂
1017	3				1072			3	
1018	4				1073			4	
1019	3	S		1074	3	S			
1020	4			CH ₂	1075			4	CH ₂
1021	3				1076			3	
1022	4				1077			4	
1023	3	S		1078	3	S			
1024	4			CH ₂	1079			4	CH ₂
1025	3				1080			3	
1026	4				1081			4	
1027	3	S		1082	3	S			
1028	4			CH ₂	1083			4	CH ₂
1029	3				1084			3	
1030	4				1085			4	
1031	3	S		1086	3	S			
1032	4			CH ₂	1087			4	CH ₂
1033	3				1088			3	
1034	4				1089			4	
1035	3	S		1090	3	S	MeS		
1036	4			CH ₂	1091			4	CH ₂
1037	3				1092			3	
1038	4				1093			4	
1039	3	S	Me	1094	3	S	MeO		
1040	4			CH ₂	1095			4	CH ₂
1041	3				1096			3	
1042	4				1097			4	

TABLE 7



Example No	n	X	R	Example No	N	X	R		
1098	3	S CH ₂		1145	3	S CH ₂			
1099	4			1146	4				
1100	3			1147	3				
1101	4			1148	4				
1102	3	S CH ₂		1149	3	S CH ₂			
1103	4			1150	4				
1104	3			1151	3				
1105	4			1152	4				
1106	3	S CH ₂		1153	3	S CH ₂			
1107	4			1154	4				
1108	3			1155	3				
1109	4			1156	4				
1110	3	S CH ₂		1157	3	S CH ₂			
1111	4			1158	4				
1112	3								
1113	4								
1114	3	S CH ₂		1159	3	S CH ₂			
1115	4			1160	4				
1116	3			1161	3				
1117	4			1162	4				
1118	3	S CH ₂		1163	3	S CH ₂			
1119	4			1164	4				
1120	3			1165	3				
1121	4			1166	4				
1122	3	S CH ₂		1167	3	S CH ₂			
1123	4			1168	4				
1124	3			1169	3				
1125	4			1170	4				
1125a	3	S CH ₂		1171	3	S CH ₂			
1126	4			1172	4				
1127	3			1173	3				
1128	4			1174	4				
1129	3	S CH ₂		1175	3	S CH ₂			
1130	4			1176	4				
1131	3			1177	3				
1132	4			1178	4				
1133	3	S CH ₂		1179	3	S CH ₂			
1134	4			1180	4				
1135	3			1181	3				
1136	4			1182	4				

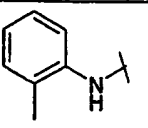
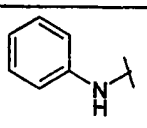
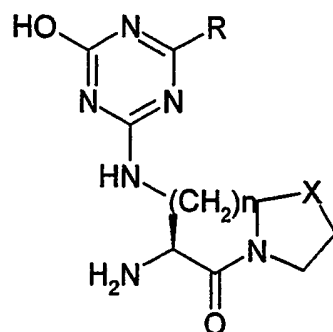
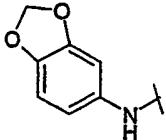
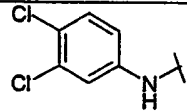
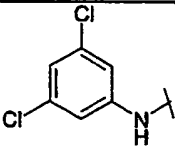
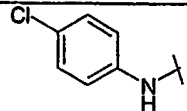
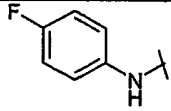
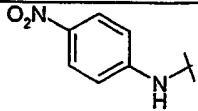
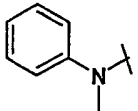
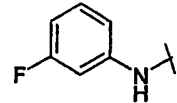
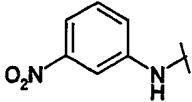
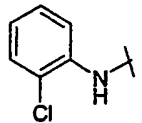
1137	3	S		1183	3	S	
1138	4			1184	4		
1139	3	CH ₂		1185	3	CH ₂	
1140	4			1186	4		
1141	3			S			
1142							
1143	3	CH ₂					
1144	4						

TABLE 8

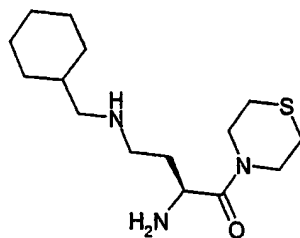


Example No	n	X	R	Example No	n	X	R
1187	3	S		1235	3	S	
1188	4	CH ₂		1236	4	CH ₂	
1189	3			1237	3		
1190	4			1238	4		
1191	3	S		1239	3	S	
1192	4	CH ₂		1240	4	CH ₂	
1193	3			1241	3		
1194	4			1242	4		
1195	3	S		1243	3	S	
1196	4	CH ₂		1244	4	CH ₂	
1197	3			1245	3		
1198	4			1246	4		
1199	3	S		1247	3	S	
1200	4	CH ₂		1248	4	CH ₂	
1201	3						
1202	4						
1203	3	S		1249	3	S	
1204	4	CH ₂		1250	4		
1205	3			1251	3		
1206	4			1252	4		

1207	3	S		1253	3	S	
1208	4			1254	4		
1209	3	CH ₂		1255	3	CH ₂	
1210	4			1256	4		
1211	3	S		1257	3	S	
1212	4			1258	4		
1213	3	CH ₂		1259	3	CH ₂	
1214	4			1260	4		
1215	3	S		1261	3	S	
1216	4			1262	4		
1217	3	CH ₂		1263	3	CH ₂	
1218	4			1264	4		
1219	3	S		1265	3	S	
1220	4			1266	4		
1221	3	CH ₂		1267	3	CH ₂	
1222	4			1268	4		
1223	3	S		1269	3	S	
1224	4			1270	4		
1225	3	CH ₂		1271	3	CH ₂	
1226	4			1272	4		
1227	3	S		1273	3	S	
1228	4			1274	4		
1229	3	CH ₂		1275	3	CH ₂	
1230	4			1276	4		
1231	3	S					
1232							
1233	3	CH ₂					
1235	4						

EXAMPLE 1277

1-[2-(S)-Amino-4-(cyclohexylmethylamino)butanoyl]thiomorpholine dihydrochloride



A. 1-[2-(S)-N-(*tert*-Butyloxycarbonyl)amino-4-(9-fluorenylmethyloxycarbonylamino)-butanoyl]thiomorpholine

1-[2-(S)-N-(*tert*-Butyloxycarbonyl)amino-4-(9-fluorenylmethyloxycarbonylamino)-butanoic acid (1.0g, 2.27mmol) was dissolved in CH₂Cl₂ /DMF (9:1, 20mL). To this solution at 0°C were added 1-hydroxybenzotriazole hydrate (461mg, 3.41mmol), water-soluble carbodiimide (521mg, 2.72mmol), thiomorpholine (281mg, 2.72mmol) and triethylamine (340mg, 3.4mmol). After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (100mL). The solution was washed with 0.3M KHSO₄ (2 x 25mL), sat. NaHCO₃ (2 x 25mL), water (2 x 25mL) and brine (1 x 25mL), dried (Na₂SO₄) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 75% ethyl acetate, 25% pet. ether) to give a white solid identified as 1-[2-(S)-N-(*tert*-butyloxycarbonyl)amino- 4-(9-fluorenylmethyloxycarbonylamino)-butanoyl]thiomorpholine (516mg, 0.98mmol, 43%).

B. 1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-4-amino)-butanoyl]thiomorpholine

1-[2-(S)-N-(*tert*-Butyloxycarbonyl)amino- 4-(9-fluorenylmethyloxycarbonylamino)-butanoyl thiomorpholine (500mg, 0.95mmol) was dissolved in tetrahydrofuran (20mL). Diethylamine (5mL) was added. After 90min at room temperature the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (eluant: 90% chloroform, 7% methanol, 3% triethylamine) to give a pale yellow oil identified as 1-[2-(S)-N-(*tert*-butyloxycarbonyl)-4-amino)-butanoyl]thiomorpholine (162mg, 0.54mmol, 56%).

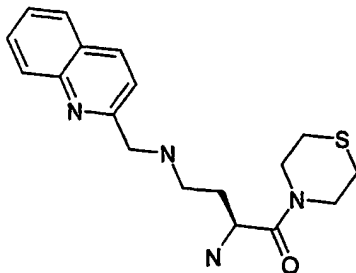
C. 1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-amino-4-(cyclohexylmethylamino)butanoyl]thiomorpholine

1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-4-amino]-butanoyl]thiomorpholine (41mg, 0.135mmol) was dissolved in dichloroethane (10mL). To this solution was added cyclohexanecarboxaldehyde (15mg, 0.135mmol). After 30mins sodium triacetoxyborohydride (32mg, 0.15mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na₂SO₄) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 1% acetic acid, 9% methanol, 90% chloroform) to give a colourless oil identified as 1-[2-(S)-N-(*tert*-butyloxycarbonyl)-amino-4-(cyclohexylmethylamino)butanoyl] thiomorpholine (25mg, 0.063mmol, 47%).

D. 1-[2-(S)-Amino-4-(cyclohexylmethylamino)butanoyl]thiomorpholine dihydrochloride

1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-amino-4-(cyclohexylmethylamino)butanoyl]thiomorpholine (25mg, 0.063mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 1-[2-(S)-amino-4-(cyclohexylmethylamino)butanoyl]thiomorpholine dihydrochloride (23mg, 0.063mmol, 100%).

$$[M+H]^+ = 300.3$$

EXAMPLE 1278**1-[2-(S)-Amino-4-((quinolin-2-ylmethyl)amino)butanoyl]thiomorpholine dihydrochloride**

A. 1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-amino-4-((quinolin-2-ylmethyl)amino)butanoyl]thiomorpholine

1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-4-amino)-butanoyl]thiomorpholine (41mg, 0.135mmol) was dissolved in 1,2-dichloroethane (10mL). To this solution was added 2-quinolinecarboxaldehyde (32mg, 0.15mmol). After 30mins sodium triacetoxymethylborohydride (36mg, 0.17mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 1% acetic acid, 9% methanol, 90% chloroform) to give a colourless oil identified as 1-[2-(S)-N-(*tert*-butyloxycarbonyl)-amino-4-((quinolin-2-ylmethyl)amino)butanoyl]thiomorpholine (32mg, 0.072mmol, 53%).

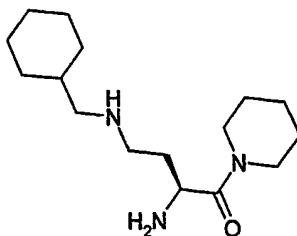
B. 1-[2-(S)-Amino-4-((quinolin-2-ylmethyl)amino)butanoyl]thiomorpholine dihydrochloride

1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-amino-4-((quinolin-2-ylmethyl)amino)butanoyl]thiomorpholine (12mg, 0.027mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 1-[2-(S)-amino-4-((quinolin-2-ylmethyl)amino)butanoyl]thiomorpholine dihydrochloride (11.3mg, 0.027mmol, 100%).

$$[\text{M}+\text{H}]^+ = 345.3$$

EXAMPLE 1279

1-[2-(S)-Amino-4-(cyclohexylmethylamino)butanoyl]piperidine dihydrochloride



A. 1-[2-(S)-N-(*tert*-Butyloxycarbonyl)amino-4-(9-fluorenylmethyloxycarbonylamino)-butanoyl] piperidine

1-[2-(S)-N-(*tert*-Butyloxycarbonyl)amino-4-(9-fluorenylmethyloxycarbonylamino)-butanoic acid (947mg, 2.154mmol) was dissolved in CH_2Cl_2 /DMF (9:1, 20mL). To this

solution at 0°C were added 1-hydroxybenzotriazole hydrate (436mg, 3.2mmol), water-soluble carbodiimide (495g, 2.58mmol), piperidine (220g, 2.58mmol) and triethylamine (320mg, 3.2mmol). After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (100mL). The solution was washed with 0.3M KHSO₄ (2 x 25mL), sat. NaHCO₃ (2 x 25mL), water (2 x 25mL) and brine (1 x 25mL), dried (Na₂SO₄) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 75% ethyl acetate, 25% pet. ether) to give a white solid identified as 1-[2-(S)-N-(*tert*-butyloxycarbonyl)amino-4-(9-fluorenylmethyloxycarbonylamino)-butanoyl]piperidine (556mg, 1.1mmol, 51%).

B. 1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-4-amino)-butanoyl]piperidine

1-[2-(S)-N-(*tert*-Butyloxycarbonyl)amino-4-(9-fluorenylmethyloxycarbonylamino)-butanoyl] piperidine (540g, 1.1mmol) was dissolved in tetrahydrofuran (20mL). Diethylamine (5mL) was added. After 90min at room temperature the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (eluant: 90% chloroform, 7% methanol, 3% triethylamine) to give a pale yellow oil identified as 1-[2-(S)-N-(*tert*-butyloxycarbonyl)-4-amino)-butanoyl] piperidine (171mg, 0.6mmol, 57%).

C. 1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-amino-4-(cyclohexylmethylamino)butanoyl] piperidine

1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-4-amino)-butanoyl] piperidine (43mg, 0.15mmol) was dissolved in 1,2-dichloroethane (20mL). To this solution was added cyclohexanecarboxaldehyde (17mg, 0.15mmol). After 30mins sodium triacetoxymethylborohydride (36mg, 0.17mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na₂SO₄) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 1% acetic acid, 9% methanol, 90% chloroform) to give a colourless oil identified as 1-[2-(S)-N-(*tert*-butyloxycarbonyl)-amino-4-(cyclohexylmethylamino)butanoyl]piperidine (38mg, 0.1mmol, 66%).

D. 1-[2-(S)-Amino-4-(cyclohexylmethylamino)butanoyl] piperidine dihydrochloride

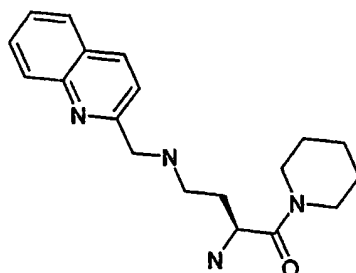
1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-amino-4-(cyclohexylmethylamino)butanoyl]piperidine (38mg, 0.1mmol) was dissolved in 4M HCl/dioxan (2mL). After 1h at room

temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 1-[2-(S)-amino-4-(cyclohexylmethylamino)butanoyl] piperidine dihydrochloride (33mg, 0.093mmol, 93%).

$[M+H]^+ = 282.3$

EXAMPLE 1280

1-[2-(S)-Amino-4-((quinolin-2-ylmethyl)amino)butanoyl]piperidine dihydrochloride



A. 1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-amino-4-((quinolin-2-ylmethyl)amino)butanoyl] piperidine

1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-4-amino)-butanoyl] piperidine (24mg, 0.15mmol) was dissolved in 1,2-dichloroethane (25mL). To this solution was added 2-quinolinecarboxaldehyde (24mg, 0.15mmol). After 30mins sodium triacetoxycarbonylborohydride (36mg, 0.17mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 1% acetic acid, 9% methanol, 90% chloroform) to give a colourless oil identified as 1-[2-(S)-N-(*tert*-butyloxycarbonyl)-amino-4-((quinolin-2-ylmethyl)amino)butanoyl] piperidine (35mg, 0.082mmol, 55%).

B. 1-[2-(S)-Amino-4-((quinolin-2-ylmethyl)amino)butanoyl] piperidine dihydrochloride

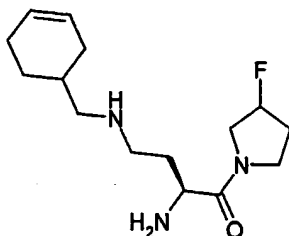
1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-amino-4-((quinolin-2-ylmethyl)amino)butanoyl] piperidine (35mg, 0.082mmol) was dissolved in 4M HCl/dioxan (2mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised

from water to give a white solid identified as 1-[2-(S)-amino-4-((quinolin-2-ylmethyl)amino)butanoyl] piperidine dihydrochloride (26mg, 0.065mmol, 79%).

$[M+H]^+ = 327.3$

EXAMPLE 1281

3-Fluoro-1-[2-(S)-amino-4-(cyclohexenylmethylamino)butanoyl]pyrrolidine dihydrochloride



A. 1-(*tert*-Butyloxycarbonyl)-3-fluoropyrrolidine

N-(*tert*-Butyloxycarbonyl)-3-hydroxypyrrolidine (21.0g, 10.7mmol) was dissolved in CH_2Cl_2 (30ml). (Diethylamino)sulphur trifluoride (1.72g, 10.7mmol) was added to this solution at -78°C . The mixture was stirred for 18 hours at -78°C to room temperature then the reaction mixture was carefully poured into sat. NaHCO_3 (100ml) and stirred for 15min and extracted with CH_2Cl_2 . The organic extract was washed with water and brine, dried (Na_2SO_4) and evaporated *in vacuo* to give an orange oil. The residue was purified by flash chromatography (eluant: 28% ethyl acetate, 72% pet. ether 60-80) to give a colourless oil identified as 1-(*tert*-butyloxycarbonyl)-3-fluoropyrrolidine (1.14g, 5.34mmol, 50%).

B 3-Fluoropyrrolidine hydrochloride

1-(*tert*-Butyloxycarbonyl)-3-fluoropyrrolidine (1.14g, 5.34mmol) was dissolved in 4M HCl /dioxan (30ml). The mixture was stirred for 1 hour at room temperature then the solvent was removed *in vacuo* to give an off-white solid identified as 3-fluoropyrrolidine hydrochloride (640mg, 5.2mmol, 95%).

C. 3-Fluoro-1-[2-(S)-N-(*tert*-butyloxycarbonyl)amino-4-(9-fluorenylmethyloxycarbonylamino)-butanoyl] pyrrolidine

1-[2-(S)-N-(*tert*-Butyloxycarbonyl)amino-4-(9-fluorenylmethyloxycarbonylamino)-butanoic acid (950mg, 2.15mmol) was dissolved in CH_2Cl_2 /DMF (9:1, 20mL). To this

solution at 0°C were added 1-hydroxybenzotriazole hydrate (395mg, 2.6mmol), water-soluble carbodiimide (572mg, 3.0mmol), 3-fluoropyrrolidine hydrochloride (270g, 2.15mmol) and triethylamine (320mg, 3.2mmol). After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (100mL). The solution was washed with 0.3M KHSO₄ (2 x 25mL), sat. NaHCO₃ (2 x 25mL), water (2 x 25mL) and brine (1 x 25mL), dried (Na₂SO₄) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 75% ethyl acetate, 25% pet. ether) to give a white solid identified as 3-fluoro-1-[2-(S)-N-(*tert*-butyloxycarbonyl)amino-4-(9-fluorenylmethyloxycarbonylamino)-butanoyl]pyrrolidine (808mg, 1.58mmol, 73%).

D. 3-Fluoro-1-[2-(S)-N-(*tert*-butyloxycarbonyl)-4-amino]-butanoyl]pyrrolidine

3-Fluoro-1-[2-(S)-N-(*tert*-butyloxycarbonyl)amino-4-(9-fluorenylmethyloxycarbonylamino)-butanoyl] pyrrolidine (800mg; 1.58mmol) was dissolved in tetrahydrofuran (20mL). Diethylamine (5mL) was added. After 90min at room temperature the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (eluant: 90% chloroform, 7% methanol, 3% triethylamine) to give a pale yellow oil identified as 3-fluoro-1-[2-(S)-N-(*tert*-butyloxycarbonyl)-4-amino]-butanoyl] pyrrolidine (316mg, 1.04mmol, 66%).

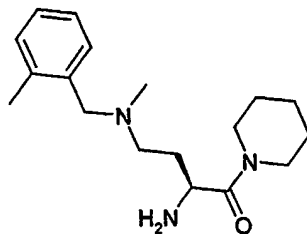
E. 3-Fluoro-1-[2-(S)-N-(*tert*-butyloxycarbonyl)-amino-4-(cyclohexenylmethylamino)butanoyl] pyrrolidine

3-Fluoro-1-[2-(S)-N-(*tert*-butyloxycarbonyl)-4-amino]-butanoyl] pyrrolidine (150mg, 0.52mmol) was dissolved in methanol (20mL). To this solution was added 3-cyclohexenecarboxaldehyde (63mg, 0.57mmol). After 30mins sodium triacetoxyborohydride (220mg, 1.04mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na₂SO₄) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 1% acetic acid, 9% methanol, 90% chloroform) to give a colourless oil identified as 3-fluoro-1-[2-(S)-N-(*tert*-butyloxycarbonyl)-amino-4-(cyclohexenylmethylamino)butanoyl]pyrrolidine (176mg, 0.46mmol, 77%).

F. 3-Fluoro-1-[2-(S)-amino-4-(cyclohexenylmethylamino)butanoyl] pyrrolidine dihydrochloride**3-Fluoro-1-[2-(S)-N-(*tert*-butyloxycarbonyl)-amino-4-**

(cyclohexenylmethylamino)butanoyl]pyrrolidine (176mg, 0.46mmol) was dissolved in 4M HCl/dioxan (2mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 3-fluoro-1-[2-(S)-amino-4-(cyclohexenylmethylamino)butanoyl] pyrrolidine dihydrochloride (140mg, 0.39mmol, 963%).

$$[M+H]^+ = 284.3$$

EXAMPLE 1282**1-[2-(S)-Amino-4-(N-methyl-N-(2-methylbenzyl)amino)butanoyl]piperidine dihydrochloride****A. N-(*tert*-Butyloxycarbonyl)-L-homoserine lactone**

L-Homoserine lactone 1.76g, 12.8mmol) was dissolved in DMF (30 mL). This solution was cooled to 0 °C, triethylamine (1.41, 14.1 mmol) di-*tert*-butyl dicarbonate(3.35g, 15.35 mmol) was added. After 18 hours at room temperature the solvent was evaporated *in vacuo*, the residue was taken up in dichloromethane (200 mL). This solution was washed with 1M KHSO₄ (2 x 50mL) and brine (1 x 50mL), dried (Na₂SO₄) and evaporated *in vacuo* to give a white solid, recrystallised from EtOAc/pet.ether to give a white solid identified as N-(*tert*-butyloxycarbonyl)-L-homoserine lactone (2.25mg, 11.2mmol, 87%).

B. 1-[2-(S)-(N-(*tert*-Butyloxycarbonyl)amino)-4-hydroxybutanoyl]piperidine

N-(*tert*-Butyloxycarbonyl)-L-homoserine lactone (100mg, 0.5mmol) was dissolved in tetrahydrofuran (30 mL). Piperidine (42mg, 0.5mmol) was added. After 72 hours at

room temperature the reaction mixture was diluted with ethyl acetate (150 mL). This solution was washed with water (1 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil identified as 1-[2-(S)-(N-(*tert*-butyloxycarbonyl)amino)-4-hydroxybutanoyl]piperidine (142mg, 0.5mmol, 100%).

C. 1-[2-(S)-(N-(*tert*-Butyloxycarbonyl)amino)-4-oxobutanoyl] piperidine

1-[2-(S)-(N-(*tert*-Butyloxycarbonyl)amino)-4-hydroxybutanoyl] piperidine (142mg, 0.5mmol) was dissolved in dichloromethane (50 mL). Dess-Martin periodinane (232mg, 0.5mmol) was added. After 1 hour at room temperature the reaction mixture was diluted with ethyl acetate (150 mL). This solution was washed with water (1 x 20ml) and brine (1 x 20ml), dried (Na_2SO_4) and evaporated *in vacuo* to give a colourless oil. Purified by flash chromatography on silica gel (eluant: 50% ethyl acetate, 50% pet. ether 60-80) to give a colourless oil identified as 1-[2-(S)-(N-(*tert*-butyloxycarbonyl)amino)-4-oxobutanoyl] piperidine (40mg, 0.14mmol, 27%).

D. 1-[2-(S)-(N-(*tert*-butyloxycarbonyl)amino)-4-(N-methyl-N-(2-methylbenzyl)amino) butanoyl]piperidine

1-[2-(S)-(N-(*tert*-Butyloxycarbonyl)amino)-4-oxobutanoyl] piperidine (40mg, 0.14mmol) was dissolved in methanol (20mL). To this solution was added N-methyl-2-methylbenzylamine (19mg, 0.14mmol). After 2 hours sodium triacetoxyborohydride (64mg, 0.3mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel to give a colourless oil identified as 1-[2-(S)-(N-(*tert*-butyloxycarbonyl)amino)-4-(N-methyl-N-(2-methylbenzyl)amino) butanoyl] piperidine (36mg, 0.09mmol, 64%).

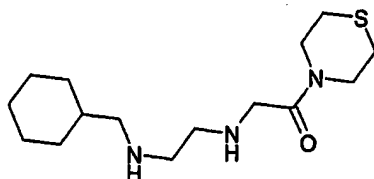
E. 1-[2-(S)-Amino-4-(N-methyl-N-(2-methylbenzyl)amino)butanoyl] piperidine dihydrochloride

1-[2-(S)-(N-(*tert*-Butyloxycarbonyl)amino)-4-(N-methyl-N-(2-methylbenzyl)amino) butanoyl] piperidine (36mg, 0.09mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a pale brown solid identified as 1-[2-(S)-amino-4-(N-

methyl-N-(2-methylbenzyl)amino)butanoyl] piperidine dihydrochloride (43mg, 0.09mmol, 100%)

EXAMPLE 1283

1-[N-(2''-(Cyclohexylmethylaminoethyl)glyciny)]thiomorpholine dihydrochloride



A. 1-[N-2'-(*tert*-Butyloxycarbonyl)-N-(2''-(9-fluorenylmethyloxycarbonyl aminoethyl)-glyciny)]thiomorpholine

N-2'-(*tert*-Butyloxycarbonyl)-N-(2''-(9-fluorenylmethyloxycarbonyl aminoethyl)-glycine (2.5g, 5.7mmol) was dissolved in CH₂Cl₂ /DMF (9:1, 100mL). To this solution at 0°C were added 1-hydroxybenzotriazole hydrate (833mg, 6.3mmol), water-soluble carbodiimide (974mg, 6.3mmol), thiomorpholine (617mg, 6.0mmol) and N-methylmorpholine (800mg, 8mmol). After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (100mL). The solution was washed with 0.3M KHSO₄ (2 x 25mL), sat. NaHCO₃ (2 x 25mL), water (2 x 25mL) and brine (1 x 25mL), dried (Na₂SO₄) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 75% ethyl acetate, 25% pet. ether) to give a white solid identified as 1-[N-2'-(*tert*-butyloxycarbonyl)-N-(2''-(9-fluorenylmethyloxycarbonyl aminoethyl)-glyciny)]thiomorpholine (2.7g, 5.1mmol, 90%).

B. 1-[N-2'-(*tert*-Butyloxycarbonyl)-(2''-aminoethyl)-glyciny] thiomorpholine

1-[N-2'-(*tert*-Butyloxycarbonyl)-N-(2''-(9-fluorenylmethyloxycarbonyl aminoethyl)-glyciny)]thiomorpholine (2.7g, 5.1mmol) was dissolved in tetrahydrofuran (20mL). Diethylamine (5mL) was added. After 90min at room temperature the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (eluant: 90% chloroform, 7% methanol, 3% triethylamine) to give a pale yellow oil identified as 1-[N-2'-(*tert*-butyloxycarbonyl)-(2''-aminoethyl)-glyciny] thiomorpholine (1.44g, 4.7mmol, 92%).

C. 1-[2'-N-(*tert*-Butyloxycarbonyl *N*-(2''-(cyclohexylmethylaminoethyl)-glyciny])]-thiomorpholine

1-[N-2'-(*tert*-Butyloxycarbonyl)-(2''-aminoethyl)-glyciny]) thiomorpholine (100mg, 0.3mmol) was dissolved in methanol (25mL). To this solution was added cyclohexanecarboxaldehyde (34mg, 0.3mmol). After 30mins sodium triacetoxymethylborohydride (126mg, 0.6mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na₂SO₄) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 1% acetic acid, 9% methanol, 90% chloroform) to give a colourless oil identified as 1-[2'-N-(*tert*-Butyloxycarbonyl *N*-(2''-(cyclohexylmethylaminoethyl)-glyciny])]-thiomorpholine (33mg, 0.08mmol, 27%).

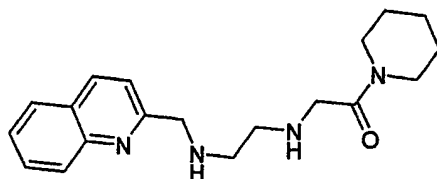
D. 1-[N-(2''-(Cyclohexylmethylaminoethyl)glyciny)]thiomorpholine dihydrochloride

1-[2'-N-(*tert*-Butyloxycarbonyl-*N*-(2''-(cyclohexylmethylaminoethyl)-glyciny])]-thiomorpholine (33mg, 0.081mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 1-[N-(2''-(cyclohexylmethylaminoethyl)glyciny)]thiomorpholine dihydrochloride (31mg, 0.08mmol, 100%).

[M+H]⁺ = 300.3

EXAMPLE 1284

1-[N-(2''-((Quinolin-2-ylmethyl)aminoethyl)glyciny)]pyrrolidine dihydrochloride



A. 1-[N-2'-(*tert*-Butyloxycarbonyl)-N-(2''-(9-fluorenylmethyloxycarbonyl aminoethyl)-glyciny)]piperidine

N-2'-(*tert*-Butyloxycarbonyl)-N-(2''-(9-fluorenylmethyloxycarbonyl aminoethyl)-glycine (2.5g, 5.7mmol) was dissolved in CH₂Cl₂ /DMF (9:1, 100mL). To this solution at 0°C were added 1-hydroxybenzotriazole hydrate (1.5g, 11.1mmol), water-soluble carbodiimide (1.3g, 6.8mmol), piperidine (484mg, 5.69mmol) and N-methylmorpholine (800mg, 8mmol). After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (100mL). The solution was washed with 0.3M KHSO₄ (2 x 25mL), sat. NaHCO₃ (2 x 25mL), water (2 x 25mL) and brine (1 x 25mL), dried (Na₂SO₄) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 75% ethyl acetate, 25% pet. ether) to give a white solid identified as 1-[N-2'-(*tert*-butyloxycarbonyl)-N-(2''-(9-fluorenylmethyloxycarbonyl aminoethyl)-glyciny)]piperidine (2.8g, 5.5mmol, 96%).

B. 1-[N-2'-(*tert*-Butyloxycarbonyl)-(2''-aminoethyl)-glyciny] piperidine

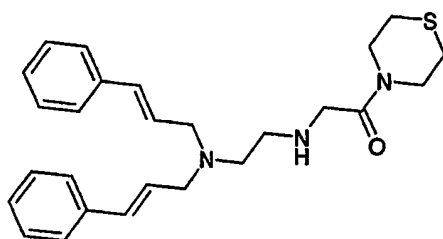
1-[N-2'-(*tert*-Butyloxycarbonyl)-N-(2''-(9-fluorenylmethyloxycarbonyl aminoethyl)-glyciny)]piperidine (2.8g, 5.5mmol) was dissolved in tetrahydrofuran (20mL). Diethylamine (5mL) was added. After 90min at room temperature the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (eluant: 90% chloroform, 7% methanol, 3% triethylamine) to give a pale yellow oil identified as 1-[N-2'-(*tert*-butyloxycarbonyl)-(2''-aminoethyl)-glyciny] piperidine (1.4g, 4.9mmol, 89%).

C. 1-[2'-N-(*tert*-Butyloxycarbonyl N-(2''-((quinolin-2-ylmethyl)aminoethyl)-glyciny)] piperidine

1-[N-2'-(*tert*-Butyloxycarbonyl)-(2''-aminoethyl)-glyciny] piperidine was dissolved in methanol (25mL). To this solution was added 2-quinolinecarboxaldehyde. After 30mins sodium triacetoxymethylborohydride was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na₂SO₄) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 1% acetic acid, 9% methanol, 90% chloroform) to give a colourless oil identified as 1-[2'-N-(*tert*-butyloxycarbonyl N-(2''-((quinolin-2-ylmethyl)aminoethyl)-glyciny)] piperidine.

D. 1-[N-(2''-((Quinolin-2-ylmethyl)aminoethyl)glyciny)]piperidine dihydrochloride

1-[2'-N-(*tert*-Butyloxycarbonyl-N-(2''-((quinolin-2-ylmethyl)aminoethyl)-glyciny)]piperidine was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 1-[N-(2''-((quinolin-2-ylmethyl)aminoethyl)glyciny)]piperidine dihydrochloride.

EXAMPLE 1285**1-[N,N-(2'',2''-((Dicinnamyl)aminoethyl)glyciny)]thiomorpholine dihydrochloride****A. 1-[2'-N-(*tert*-Butyloxycarbonyl N,N-(2'',2''-((dicinnamyl)aminoethyl)-glyciny)]thiomorpholine**

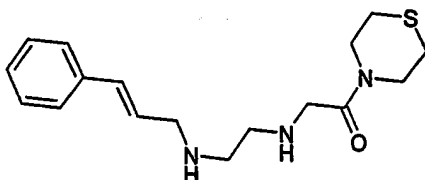
(2S)-1-(*N*^t-(*tert*-Butyloxycarbonyl)-L-lysiny)-pyrrolidine-2-carbonitrile (250mg, 0.83mmol) was dissolved in dichloroethane (25mL). To this solution was added trans-cinnamaldehyde (108mg, 0.83mmol). After 30mins sodium triacetoxymethylborohydride (350mg, 1.6mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na₂SO₄) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 2% methanol, 98% chloroform) to give a colourless oil identified as 1-[2'-N-(*tert*-butyloxycarbonyl N,N-(2'',2''-((dicinnamyl)aminoethyl)-glyciny)] thiomorpholine. Further elution with 9% methanol, 90% chloroform and 1% acetic acid gave a colourless oil identified as 1-[2'-N-(*tert*-butyloxycarbonyl N,N-(2''-((cinnamyl)aminoethyl)-glyciny)] thiomorpholine (180mg, 0.43mmol, 52%)

B. 1-[N,N-(2'',2''-((Dicinnamyl)aminoethyl)glyciny)]thiomorpholine dihydrochloride

1-[2'-N-(*tert*-Butyloxycarbonyl N,N-(2'',2''-((dicinnamyl)aminoethyl)-glyciny)] thiomorpholine was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 1-[N,N-(2'',2''-((dicinnamyl)aminoethyl)glyciny)]thiomorpholine dihydrochloride.

EXAMPLE 1286

1-[N-(2''-((Cinnamyl)aminoethyl)glyciny)]thiomorpholine dihydrochloride



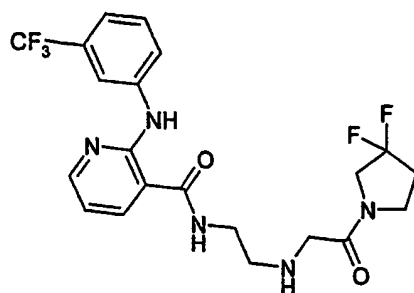
A. 1-[N-(2''-((Cinnamyl)aminoethyl)glyciny)]thiomorpholine dihydrochloride

1-[2'-N-(*tert*-Butyloxycarbonyl N-(2''-((cinnamyl)aminoethyl)-glyciny)] thiomorpholine (180mg, 0.43mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 1-[N-(2''-((cinnamyl)aminoethyl)glyciny)]thiomorpholine dihydrochloride (168mg, 0.43mmol, 100%).

$$[M+H]^+ = 320.3$$

EXAMPLE 1287

3,3-Difluoro-1-[N-2''-(3'-trifluoromethylanilino)pyridyl-3-carbonyl aminoethyl)glyciny)]pyrrolidine dihydrochloride



A. 3,3-Difluoro-1-[N-2'-(*tert*-butyloxycarbonyl)-N-(2''-(9-fluorenylmethyloxycarbonyl)aminoethyl)-glyciny] pyrrolidine

N-2'-(*tert*-Butyloxycarbonyl)-N-(2''-(9-fluorenylmethyloxycarbonyl)aminoethyl)-glycine (1.0g, 2.27mmol) was dissolved in CH₂Cl₂ /DMF (9:1, 100mL). To this solution at 0°C were added 1-hydroxybenzotriazole hydrate (620mg, 4.6mmol), water-soluble carbodiimide (560mg, 2.8mmol), 3,3-difluoropyrrolidine hydrochloride (360mg, 2.5mmol) and N-methylmorpholine (800mg, 8mmol). After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (100mL). The solution was washed with 0.3M KHSO₄ (2 x 25mL), sat. NaHCO₃ (2 x 25mL), water (2 x 25mL) and brine (1 x 25mL), dried (Na₂SO₄) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 60% ethyl acetate, 40% pet. ether) to give a white solid identified as 3,3-difluoro-1-[N-2'-(*tert*-butyloxycarbonyl)-N-(2''-(9-fluorenylmethyloxycarbonyl)aminoethyl)-glyciny] pyrrolidine (934g, 1.7mmol, 77%).

B. 3,3-Difluoro-1-[N-2'-(*tert*-butyloxycarbonyl)aminoethyl)-glyciny] pyrrolidine

3,3-Difluoro-1-[N-2'-(*tert*-butyloxycarbonyl)-N-(2''-(9-fluorenylmethyloxycarbonyl)aminoethyl)-glyciny] pyrrolidine (890g, 1.68mmol) was dissolved in tetrahydrofuran (20mL). Diethylamine (5mL) was added. After 90min at room temperature the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (eluant: 90% chloroform, 7% methanol, 3% triethylamine) to give a pale yellow oil identified as 3,3-difluoro-1-[N-2'-(*tert*-butyloxycarbonyl)aminoethyl)-glyciny] pyrrolidine (470mg, 1.5mmol, 91%).

C. 3,3-Difluoro-1-[N-2'-(*tert*-butyloxycarbonyl)-N-2''-(3'-trifluoromethylanilino)pyridyl-3-carbonyl aminoethyl)glyciny]pyrrolidine

3,3-Difluoro-1-[N-2'-(*tert*-butyloxycarbonyl)aminoethyl)-glyciny] pyrrolidine (50mg, 0.16mmol) was dissolved in CH₂Cl₂ /DMF (9:1, 20mL). To this solution at 0°C was

added 1-hydroxybenzotriazole hydrate (46mg, 0.34mmol), water-soluble carbodiimide (40mg, 0.2mmol), niflumic acid (49mg, 0.17mmol) and N-methylmorpholine (40mg, 0.4mmol). After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (70mL). The solution was washed with 0.3M KHSO₄ (1 x 20mL), sat. NaHCO₃ (1 x 20mL), water (1 x 20mL) and brine (1 x 20mL), dried (Na₂SO₄) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 75% ethyl acetate, 25% pet. ether) to give a yellow oil identified as 3,3-difluoro-1-[N-2''-(*tert*-butyloxycarbonyl)-N-2''-(3'-trifluoromethylanilino)pyridyl-3-carbonyl aminoethyl)glyciny]]pyrrolidine (63mg, 0.11mmol, 67%).

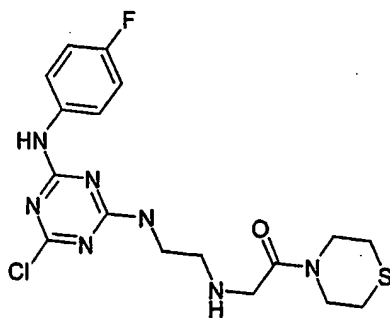
D. 3,3-Difluoro-1-[N-2''-(3'-trifluoromethylanilino)pyridyl-3-carbonyl aminoethyl)glyciny]]pyrrolidine dihydrochloride

3,3-Difluoro-1-[N-2''-(*tert*-butyloxycarbonyl)-N-2''-(3'-trifluoromethylanilino)pyridyl-3-carbonyl aminoethyl)glyciny]]pyrrolidine (55mg, 0.10mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a pale brown solid identified as 3,3-difluoro-1-[N-2''-(3'-trifluoromethylanilino)pyridyl-3-carbonyl aminoethyl)glyciny]]pyrrolidine dihydrochloride (52mg, 0.10mmol, 100%).

$$[M+H]^+ = 472.3$$

EXAMPLE 1288

3,3-Difluoro-[N-2''-(6-Chloro-4-(4'-fluoroanilino)-1,3,5-triazinyl)aminoethyl)glyciny]]thiomorpholine dihydrochloride



A. 4,6-Dichloro-2-(4'-fluoroanilino)-1,3,5-triazine

Cyanuric chloride (1.844g, 10mmol) was dissolved in acetonitrile (20mL). The solution was cooled to -20°C . A solution of 4-fluoroaniline (1.1g, 10mmol) and triethylamine (1.0g, 10mmol) was slowly added. After 1 hour at -20°C the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (150mL). The solution was washed with water (1 x 50mL) and brine (1 x 50mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was recrystallised from ethyl acetate/ hexane to give an off white solid identified as 4,6-dichloro-2-(4'-fluoroanilino)-1,3,5-triazine 1.7g, 6.0mmol, 60%).

B. 1-[N-2'-(tert-butyloxycarbonyl)-N-2''-(6-Chloro-4-(4'-fluoroanilino)-1,3,5-triazinyl aminoethyl)glyciny]] thiomorpholine

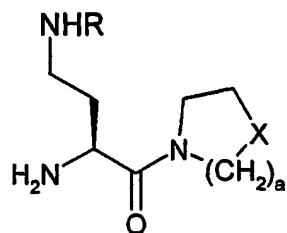
1-[N-2'-(tert-butyloxycarbonyl)aminoethyl]-glyciny]] thiomorpholine (100mg, 0.3mmol) was dissolved in dichloromethane (30mL). To this solution was added 4,6-dichloro-2-(4'-fluoroanilino)-1,3,5-triazine (90mg, 0.3mmol) and triethylamine (50mg, 0.5mmol). After 2 hours at room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (150mL). This solution was washed with water (2 x 30mL) and brine (1 x 30mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography (eluant: 60% ethyl acetate, 40% pet. ether) to give a white solid identified as 1-[N-2'-(tert-butyloxycarbonyl)-N-2''-(6-chloro-4-(4'-fluoroanilino)-1,3,5-triazinyl aminoethyl)glyciny]] thiomorpholine (20mg, 0.032mmol, 11%).

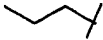
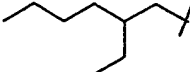
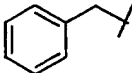
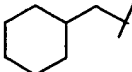
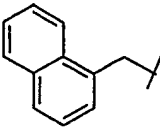
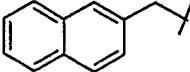
C. 1-[N-2''-(6-Chloro-4-(4'-fluoroanilino)-1,3,5-triazinyl)aminoethyl) glyciny]] thiomorpholine dihydrochloride

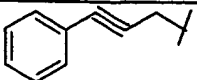
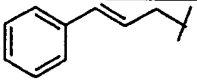
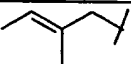
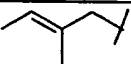
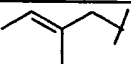
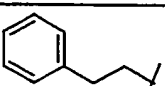
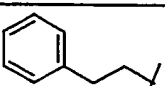
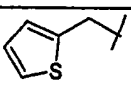
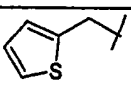
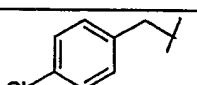
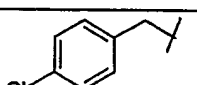
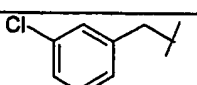
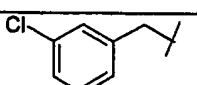
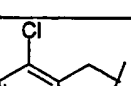
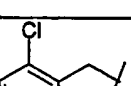
1-[N-2'-(tert-butyloxycarbonyl)-N-2''-(6-chloro-4-(4'-fluoroanilino)-1,3,5-triazinyl aminoethyl)glyciny]] thiomorpholine (18.8mg, 0.03mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 1-[N-2''-(6-Chloro-4-(4'-fluoroanilino)-1,3,5-triazinyl)aminoethyl) glyciny]] thiomorpholine dihydrochloride (18mg, 0.03mmol, 100%).

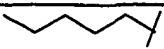
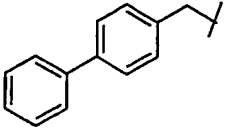
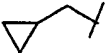
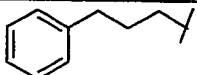
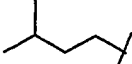
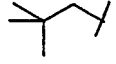
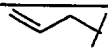
$[\text{M}+\text{H}]^+ = 526.4$

TABLE 9



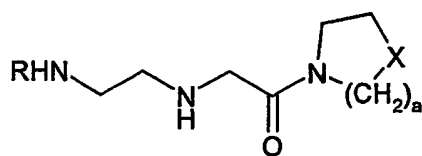
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1296	CF ₂		
1297	CHF		
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1299	CH ₂		
1300	O		
1311	S	1	
1312	CF ₂		
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1315	CH ₂		
1316	O		
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1318	CF ₂		
1319	CHF		
1320	O	2	
1321	S	1	
1322	CF ₂		
1323	CHF		
1324	S	2	
1325	CH ₂		
1326	O		
1327	S	1	
1328	CF ₂		
1329	CHF		
1330	S	2	
1331	CH ₂		
1332	O		
1333	S	1	

1334	CF ₂	2	
1335	CHF		
1336	S		
1337	CH ₂		
1338	O		
1339	S	1	
1340	CF ₂		
1341	CHF		
1342	S	2	
1343	CH ₂		
1344	O		
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1349	CH ₂		
1350	O		
1351	S	1	
1352	CF ₂		
1353	CHF		
1354	S	2	
1355	CH ₂		
1356	O		
1357	S	1	
1358	CF ₂		
1359	CHF		
1360	S	2	
1361	CH ₂		
1362	O		
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1364	CF ₂		
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1367	CH ₂		
1368	O		
1369	S	1	
1370	CF ₂		
1371	CHF		
1372	S	2	
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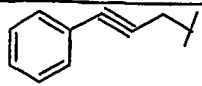
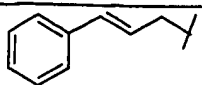
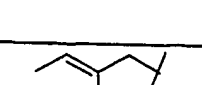

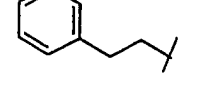
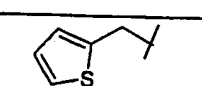
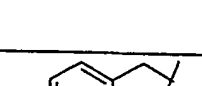
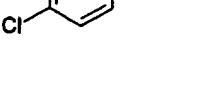
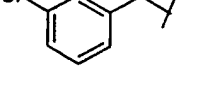
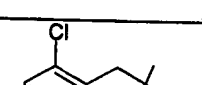
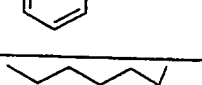

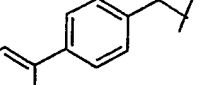
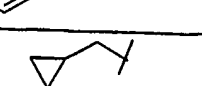
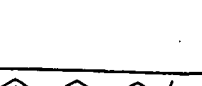
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1388	CF ₂		
1389	CHF		
1390	S	2	
1391	CH ₂		
1392	O		
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1395	CHF		
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1397	CH ₂		
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1400	CF ₂		
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1416	O		
1417	S	1	
1418	CF ₂		
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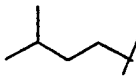
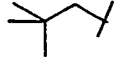
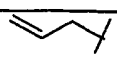
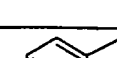
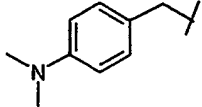
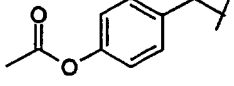
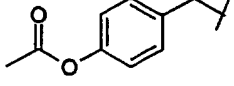
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1433	CH ₂		
1434	O		

TABLE 10



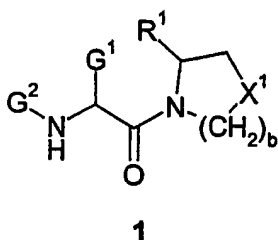
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1621	CH ₂		
1622	S		
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1625	CH ₂		
1626	S	2	
1627	CF ₂		
1628	S		
1629	CH ₂	1	
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1631	CF ₂		
1632	S	2	
1633	CH ₂		
1634	S		
1635	CF ₂	1	
1636	S		
1637	CH ₂		
1638	S	2	

1639	CF ₂		2	
1640	S			
1641	CH ₂			
1642	S		1	
1643	CF ₂			
1644	S			
1645	CH ₂		2	
1646	S			
1647	CF ₂			
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1677	CH ₂			
1678	S		2	
1679	CF ₂			
1680	S			
1681	CH ₂		1	
1682	S			
1683	CF ₂			
1684	S		2	

1685	CH ₂		
1686	S	1	
1687	CF ₂		
1688	S	2	
1689	CH ₂		
1690	S	1	
1691	CF ₂		
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1693	CH ₂		
1694	S	1	
1695	CF ₂		
1696	S	2	
1697	CH ₂		
1698	S	1	
1699	CF ₂		
1700	S	2	
1701	CH ₂		
1702	S	1	
1703	CF ₂		
1704	S	2	
1705	CH ₂		

CLAIMS

- 1 A compound according to general formula 1, or a pharmaceutically acceptable salt thereof,

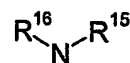
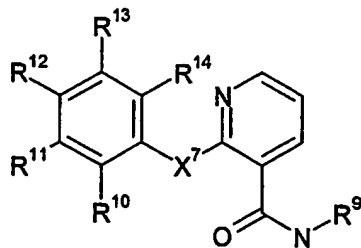
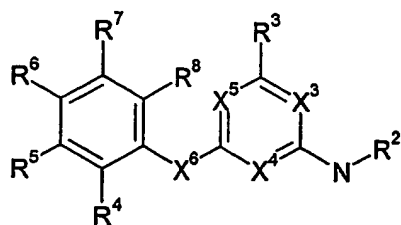


wherein:

either G^1 is $-\text{CH}_2-\text{X}^2-(\text{CH}_2)_a-\text{G}^3$ and G^2 is H, or

G^2 is $-\text{CH}_2-(\text{CH}_2)_a-\text{G}^3$ and G^1 is H;

G^3 is selected from a group according to general formula 2, a group according to general formula 3, and a group according to general formula 4;



a is 0, 1 or 2;

b is 1 or 2;

X^1 is selected from CH_2 , S, CF_2 , CHF, $\text{CH}(\text{CH}_3)$, $\text{C}(\text{CH}_3)_2$, $\text{CH}(\text{CN})$ and O;

X^2 is selected from CH_2 , O and S, provided that if a is 1 then X^2 is CH_2 ;

X^3 , X^4 and X^5 are selected from N and CH, provided that at least two of X^3 , X^4 and X^5 are N;

X^6 is selected from O and NH;

X^7 is selected from CH_2 , O, S and NH;

R^1 is selected from H and CN;

R^2 is selected from H and alkyl;

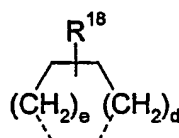
R^3 is selected from H, Cl, OH, O-alkyl, NH_2 , NH-alkyl and $N(alkyl)_2$;

R^4 , R^5 , R^6 , R^7 and R^8 are independently selected from H, Br, Cl, F, CF_3 , alkyl, acyl, OH, O-alkyl, NH_2 , NH-alkyl, $N(alkyl)_2$, NO_2 , NH-acyl, CO_2H , CO_2 -alkyl, $CONH_2$, CONH-alkyl, $CON(alkyl)_2$ and CN;

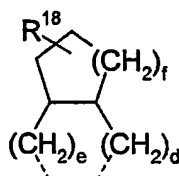
R^9 is selected from H and alkyl;

R^{10} , R^{11} , R^{12} , R^{13} and R^{14} are independently selected from H, Br, Cl, F, CF_3 , alkyl, acyl, OH, O-alkyl, NH_2 , NH-alkyl, $N(alkyl)_2$, NO_2 , NH-acyl, CO_2H , CO_2 -alkyl, $CONH_2$, CONH-alkyl, $CON(alkyl)_2$ and CN;

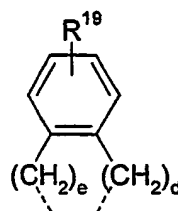
R^{15} and R^{16} are independently selected from H, alkyl, alkenyl, polyfluoroalkyl, aralkyl, aryl and $-CH_2-L-R^{17}$, or R^{15} and R^{16} together form a group according to general formula 5, general formula 6 or general formula 7;



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R^{17} is selected from H, alkyl and aryl;

R^{18} is selected from H, alkyl, aryl, OH, O-alkyl, NH_2 , NH-alkyl and $N(alkyl)_2$;

R^{19} is selected from H, alkyl, aryl, F, Cl, Br, CF_3 , OH, O-alkyl, NH_2 , NH-alkyl and $N(alkyl)_2$;

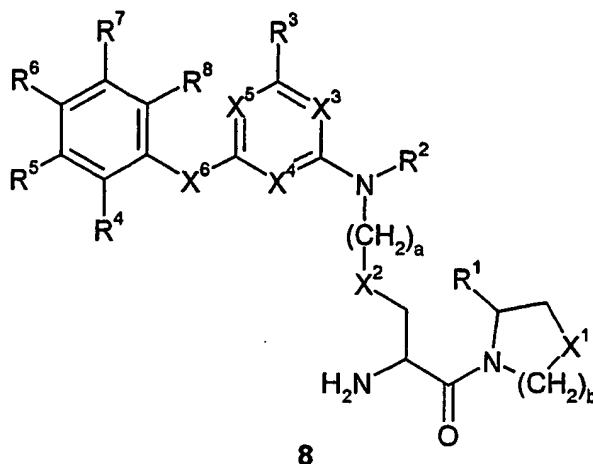
L is selected from a covalent bond, $CH=CH$, $C\equiv C$ and $-C_6H_4-$;

d and e are selected from 0, 1, 2 and 3 such that $d+e$ is 3, 4 or 5; and

f is selected from 1, 2 and 3;

provided that when R^{15} and R^{16} are both H and b is 1 then X^1 is not S or CH_2 .

- 2 A compound according to general formula 8, or a pharmaceutically acceptable salt thereof,



wherein:

a is 0, 1 or 2;

b is 1 or 2;

X¹ is selected from CH₂, S, CF₂, CHF, CH(CH₃), C(CH₃)₂, CH(CN) and O;

X² is selected from CH₂, O and S, provided that if **a** is 1 then **X²** is CH₂;

X³, **X⁴** and **X⁵** are selected from N and CH, provided that at least two of **X³**, **X⁴** and **X⁵** are N;

X⁶ is selected from O and NH;

R¹ is selected from H and CN;

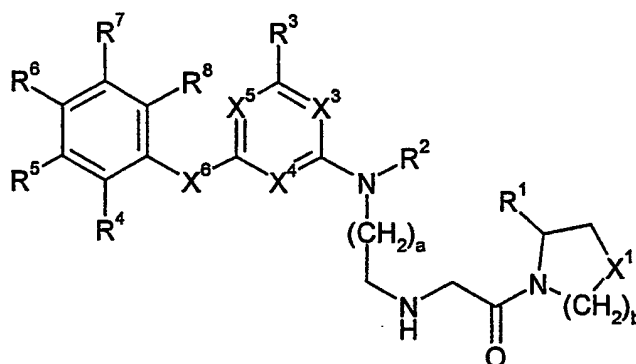
R² is selected from H and alkyl;

R³ is selected from H, Cl, OH, O-alkyl, NH₂, NH-alkyl and N(alkyl)₂;

R⁴, **R⁵**, **R⁶**, **R⁷** and **R⁸** are independently selected from H, Br, Cl, F, CF₃, alkyl, acyl, OH, O-alkyl, NH₂, NH-alkyl, N(alkyl)₂, NO₂, NH-acyl, CO₂H, CO₂-alkyl, CONH₂, CONH-alkyl, CON(alkyl)₂ and CN.

- 3 A compound according to Claim 2 wherein **R¹** is H.
- 4 A compound according to Claim 2 wherein **R¹** is CN.
- 5 A compound according to any of Claims 2 to 4 wherein **X¹** is CH₂.
- 6 A compound according to any of Claims 2 to 4 wherein **X¹** is S.
- 7 A compound according to any of Claims 2 to 6 wherein **b** is 1.

- 8 A compound according to any of Claims 2 to 6 wherein b is 2.
- 9 A compound according to any of Claims 2 to 8 wherein a is 1.
- 10 A compound according to any of Claims 2 to 8 wherein a is 2 and X^2 is CH_2 .
- 11 A compound according to any of Claims 2 to 10 wherein X^3 , X^4 and X^5 are all N.
- 12 A compound according to general formula 9, or a pharmaceutically acceptable salt thereof,



9

wherein:

a is 1 or 2;

b is 1 or 2;

X^1 is selected from CH_2 , S, CF_2 , CHF, $\text{CH}(\text{CH}_3)$, $\text{C}(\text{CH}_3)_2$, $\text{CH}(\text{CN})$ and O;

X^3 , X^4 and X^5 are selected from N and CH, provided that at least two of X^3 , X^4 and X^5 are N;

X^6 is selected from O and NH;

R^1 is selected from H and CN;

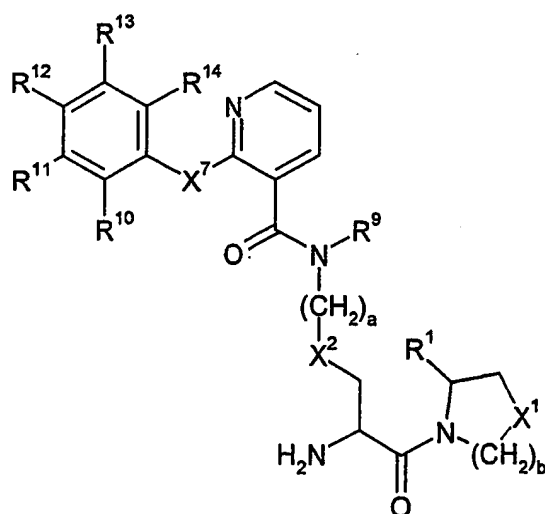
R^2 is selected from H and alkyl;

R^3 is selected from H, Cl, OH, O-alkyl, NH_2 , NH-alkyl and $\text{N}(\text{alkyl})_2$;

R^4 , R^5 , R^6 , R^7 and R^8 are independently selected from H, Br, Cl, F, CF_3 , alkyl,

acyl, OH, O-alkyl, NH₂, NH-alkyl, N(alkyl)₂, NO₂, NH-acyl, CO₂H, CO₂-alkyl, CONH₂, CONH-alkyl, CON(alkyl)₂ and CN.

- 13 A compound according to Claim 12 wherein R¹ is H.
- 14 A compound according to Claim 12 wherein R¹ is CN.
- 15 A compound according to any of Claims 12 to 14 wherein X¹ is CH₂.
- 16 A compound according to any of Claims 12 to 14 wherein X¹ is S.
- 17 A compound according to any of Claims 12 to 16 wherein b is 1.
- 18 A compound according to any of Claims 12 to 16 wherein b is 2.
- 19 A compound according to any of Claims 12 to 18 wherein a is 1.
- 20 A compound according to any of Claims 12 to 19 wherein X³, X⁴ and X⁵ are all N.
- 21 A compound according to general formula 10, or a pharmaceutically acceptable salt thereof,



10

wherein:

a is 0, 1 or 2;

b is 1 or 2;

X¹ is selected from CH₂, S, CF₂, CHF, CH(CH₃), C(CH₃)₂, CH(CN) and O;

X² is selected from CH₂, O and S, provided that if a is 1 then X² is CH₂;

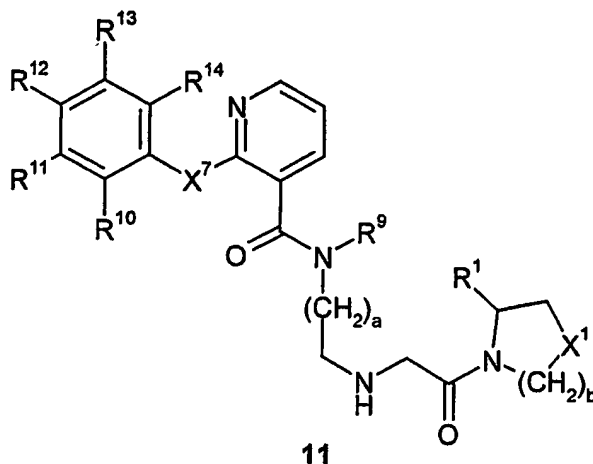
X⁷ is selected from O, S, CH₂ and NH;

R¹ is selected from H and CN;

R⁹ is selected from H and alkyl;

R¹⁰, R¹¹, R¹², R¹³ and R¹⁴ are independently selected from H, Br, Cl, F, CF₃, alkyl, acyl, OH, O-alkyl, NH₂, NH-alkyl, N(alkyl)₂, NO₂, NH-acyl, CO₂H, CO₂-alkyl, CONH₂, CONH-alkyl, CON(alkyl)₂ and CN is selected from H, Cl, OH, O-alkyl, NH₂, NH-alkyl and N(alkyl)₂.

- 22 A compound according to Claim 21 wherein R¹ is H.
- 23 A compound according to Claim 21 wherein R¹ is CN.
- 24 A compound according to any of Claims 21 to 23 wherein X¹ is CH₂.
- 25 A compound according to any of Claims 21 to 23 wherein X¹ is S.
- 26 A compound according to any of Claims 21 to 25 wherein b is 1.
- 27 A compound according to any of Claims 21 to 25 wherein b is 2.
- 28 A compound according to any of Claims 21 to 27 wherein a is 1.
- 29 A compound according to any of Claims 21 to 27 wherein a is 2 and X² is CH₂.
- 30 A compound according to general formula 11, or a pharmaceutically acceptable salt thereof,



wherein:

a is 1 or 2;

b is 1 or 2;

X¹ is selected from CH₂, S, CF₂, CHF, CH(CH₃), C(CH₃)₂, CH(CN) and O;

X⁷ is selected from O, S, CH₂ and NH;

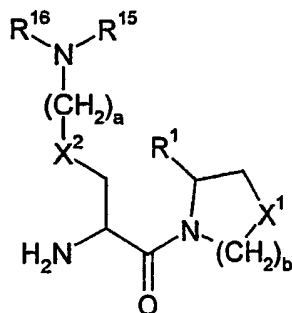
R¹ is selected from H and CN;

R⁹ is selected from H and alkyl;

R¹⁰, R¹¹, R¹², R¹³ and R¹⁴ are independently selected from H, Br, Cl, F, CF₃, alkyl, acyl, OH, O-alkyl, NH₂, NH-alkyl, N(alkyl)₂, NO₂, NH-acyl, CO₂H, CO₂-alkyl, CONH₂, CONH-alkyl, CON(alkyl)₂ and CN is selected from H, Cl, OH, O-alkyl, NH₂, NH-alkyl and N(alkyl)₂.

- 31 A compound according to Claim 30 wherein R¹ is H.
- 32 A compound according to Claim 30 wherein R¹ is CN.
- 33 A compound according to any of Claims 30 to 32 wherein X¹ is CH₂.
- 34 A compound according to any of Claims 30 to 32 wherein X¹ is S.
- 35 A compound according to any of Claims 30 to 34 wherein b is 1.
- 36 A compound according to any of Claims 30 to 34 wherein b is 2.

- 37 A compound according to any of Claims 30 to 36 wherein a is 1.
- 38 A compound according to general formula 12, or a pharmaceutically acceptable salt thereof,



12

wherein:

a is 0, 1 or 2;

b is 1 or 2;

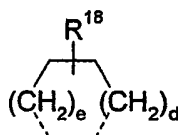
X¹ is selected from CH₂, S, CF₂, CHF, CH(CH₃), C(CH₃)₂, CH(CN) and O;

X² is selected from CH₂, O and S, provided that if a is 1 then X² is CH₂;

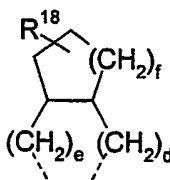
R¹ is selected from H and CN;

R¹⁵ and R¹⁶ are each independently selected from H, alkyl, alkenyl, polyfluoroalkyl, aralkyl, aryl and CH₂-L-R¹⁷;

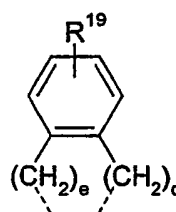
or R¹⁵ and R¹⁶ together are a group according to general formula 5, a group according to general formula 6 or a group according to general formula 7;



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R¹⁷ is selected from H, alkyl and aryl;

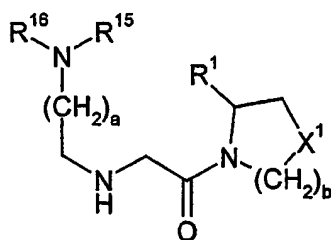
R¹⁸ is selected from H, alkyl, aryl, OH, O-alkyl, NH₂, NH-alkyl and N(alkyl)₂;

R¹⁹ is selected from H, alkyl, aryl, F, Cl, Br, CF₃, OH, O-alkyl, NH₂, NH-alkyl and N(alkyl)₂;

L is selected from a covalent bond, CH=CH, C≡C and -C₆H₄-;

d and e are selected from 0, 1, 2 and 3 such that d+e is 3, 4 or 5; and
 f is selected from 1, 2 and 3;
 provided that when R¹⁵ and R¹⁶ are both H and b is 1 then X¹ is not S or CH₂.

- 39 A compound according to Claim 38 wherein R¹ is H.
- 40 A compound according to Claim 38 wherein R¹ is CN.
- 41 A compound according to any of Claims 38 to 40 wherein X¹ is CH₂.
- 42 A compound according to any of Claims 38 to 40 wherein X¹ is S.
- 43 A compound according to any of Claims 38 to 42 wherein b is 1.
- 44 A compound according to any of Claims 38 to 42 wherein b is 2.
- 45 A compound according to any of Claims 38 to 44 wherein a is 1.
- 46 A compound according to any of Claims 38 to 44 wherein a is 2 and X² is CH₂.
- 47 A compound according to general formula 13, or a pharmaceutically acceptable salt thereof,



13

wherein:

a is 1 or 2;

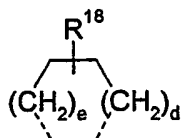
b is 1 or 2;

X^1 is selected from CH_2 , S, CF_2 , CHF, $CH(CH_3)$, $C(CH_3)_2$, $CH(CN)$ and O;

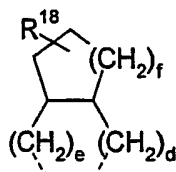
R^1 is selected from H and CN;

R^{15} and R^{16} are each independently selected from H, alkyl, alkenyl, polyfluoroalkyl, aralkyl, aryl and CH_2-L-R^{17} ;

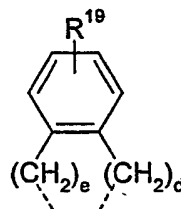
or R^{15} and R^{16} together are a group according to general formula 5, a group according to general formula 6 or a group according to general formula 7;



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R^{17} is selected from H, alkyl and aryl;

R^{18} is selected from H, alkyl, aryl, OH, O-alkyl, NH_2 , NH-alkyl and $N(alkyl)_2$;

R^{19} is selected from H, alkyl, aryl, F, Cl, Br, CF_3 , OH, O-alkyl, NH_2 , NH-alkyl and $N(alkyl)_2$;

L is selected from a covalent bond, $CH=CH$, $C\equiv C$ and $-C_6H_4-$;

d and e are selected from 0, 1, 2 and 3 such that d+e is 3, 4 or 5; and

f is selected from 1, 2 and 3.

- 48 A compound according to Claim 47 wherein R^1 is H.
- 49 A compound according to Claim 47 wherein R^1 is CN.
- 50 A compound according to any of Claims 47 to 49 wherein X^1 is CH_2 .
- 51 A compound according to any of Claims 47 to 49 wherein X^1 is S.
- 52 A compound according to any of Claims 47 to 51 wherein b is 1.
- 53 A compound according to any of Claims 47 to 51 wherein b is 2.
- 54 A compound according to any of Claims 47 to 53 wherein a is 1.
- 55 A pharmaceutical composition comprising a compound according to any of

Claims 1 to 54.

- 56 A use for a compound according to any of Claims 1 to 54, which is as a component in the preparation of a pharmaceutical composition.
- 57 A method of treatment of disease in a human or animal subject, comprising a step of administering to the subject a therapeutically active amount of a compound according to any of Claims 1 to 54
- 58 A method of treatment according to claim 57 where the disease is caused by dysregulation of a post-proline cleaving proteases or their endogenous substrates.
- 59 A method of treatment according to claim 57 where the disease is ameliorated by inhibition of a post-proline cleaving proteases.
- 60 A method of treatment according to claim 57 where the disease is caused by dysregulation of a post-proline cleaving proteases or its endogenous substrates which is an intracellular protease.
- 61 A composition according to claim 1 or 38 with the proviso that when $X^1 = S$; $b = 1$; $R^1 = H$; $G^2 = H$; G^1 is $-CH_2-X^2-(CH_2)_a-G^3$; $a = 1$, $X^2 = CH_2$; $G^3 = NR^{15}R^{16}$; and one of R^{15} , $R^{16} = H$, the other of R^{15} , R^{16} is not pyridyl, substituted pyridyl, pyrazinyl or substituted pyrazinyl.
- 62 A composition according to claim 1, 38, 47 or 61 with the proviso that when $b=1$, R^1 is H and X^1 is S; $G^1 = H$; G^2 is $-CH_2-(CH_2)_a-G^3$; $a = 1$; G^3 is $NR^{15}R^{16}$ and one of R^{15} and R^{16} is H the other of R^{15} , R^{16} is not pyridyl, substituted pyridyl, pyrazinyl or substituted pyrazinyl.
- 63 A composition according to claim 1, 38, 47, 61 or 62 with the proviso that when $b=1$, R^1 is CN and X^1 is CH_2 ; $G^1 = H$; G^2 is $-CH_2-(CH_2)_a-G^3$; $a = 1$; G^3 is $NR^{15}R^{16}$ and one of R^{15} and R^{16} is H, the other of R^{15} , R^{16} is not pyridyl, substituted pyridyl, pyrazinyl or substituted pyrazinyl.

- 64 A composition according to claim 1, 38, 47, 61, 62 or 63 with the proviso that when $G^2 = H$; $G^1 = -CH_2-X^2-(CH_2)_a-G^3$; X^2 is CH_2 ; $a = 1$; $G^3 = NR^{15}R^{16}$ and $R^{15} = R^{16} = H$; b is not 2 when X^1 is O or CH_2 , and b is not 1 when X^1 is CH_2 .
- 65 A method of treatment according to claim 57 in which the disease is caused by dysregulation of a non-membrane associated post-proline cleaving proteases such as QPP, DPP-8 and DPP-9 enzymes or their endogenous substrates.
- 66 A method of treatment according to claim 57 in which the disease is ameliorated by inhibition of a non-membrane associated post-proline cleaving proteases such as QPP, DPP-8 and DPP-9 enzymes or their endogenous substrates.
- 67 A method according to claim 65 or 66 in which the compound is a selective inhibitor of non-membrane associated post-proline cleaving proteases.

INTERNATIONAL SEARCH REPORT

International Application No

PCT. 02/04764

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/40 C07D207/16 C07D277/04 C07D295/18 C07D207/10
 C07D417/12 C07D401/12 C07D409/12 C07D403/12 C07D405/12
 A61K31/426 A61K31/427 A61K31/53 A61K31/54 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 011 155 A (VILLHAUER EDWIN BERNARD) 4 January 2000 (2000-01-04) cited in the application column 1 -column 2 examples 35,63 -----	1-37, 55-67

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

10 December 2002

Date of mailing of the international search report

Name and mailing address of the ISA

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 NL - 2280 HV Rijswijk
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Authorized officer

Kollmannsberger, M

INTERNATIONAL SEARCH REPORT

Inte

ial application No.
T/GB 02/04764

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 57-60, 65-67 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1 (partly); 2-37; 55-67 (partly)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1 (partly); 2-37; 55-67 (partly)

Glycine substituted saturated N-containing heterocycles as defined in claim 1, substituted via a methylene containing chain by nitrogen bound biaryl moieties (defined as structures 2 or 3), corresponding compositions and uses

2. Claims: 1 (partly); 38-46; 55-60 (partly); 61; 62-67 (partly)

Glycine substituted saturated N-containing heterocycles as defined in claim 1, substituted via a methylene containing chain by nitrogen bound substituents (defined as structure 4) in position G1 with G2=H, corresponding compositions and uses

3. Claims: 1 (partly); 47-54; 55-60 (partly); 62-67 (partly)

Glycine substituted saturated N-containing heterocycles as defined in claim 1, substituted via a methylene containing chain by nitrogen bound substituents (defined as structure 4) in position G2 with G1=H, corresponding compositions and uses

ation on patent family members

PCT/ 02/04764

Form PCT/ISA/210 (patent family annex) (July 1992)